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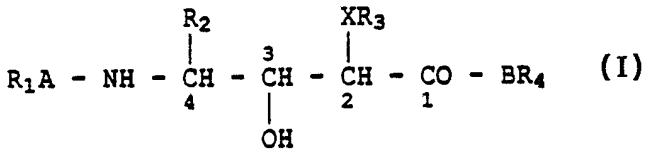
(54) Title: 4-AMINO-3-HYDROXYCARBOXYLIC ACID DERIVATIVES



(I)

(57) Abstract

The invention concerns the compounds of formula (I) wherein A and B independently are a bond or optionally substituted aminoacyl; R_1 is hydrogen; an amino protecting group; or a group of formula R_6Y- wherein R_6 is hydrogen or an optionally substituted alkyl, alkenyl, alkinyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl group; and Y is -CO-; -NHCO-; NHCS-; -SO_2-; -O-CO-; or -O-CS-; R_2 is the side chain of a natural amino acid; an alkyl, arylalkyl, heteroarylalkyl or cycloalkylalkyl group; or trimethylsilylmethyl, 2-thienylmethyl or styrylmethyl; R_3 is an optionally substituted alkyl, alkenyl, alkinyl, cyloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl group; R_4 is a group of formula -OR_7 or -NHR_7 wherein R_7 has the significance indicated above for R_6; and X is -S- or -NR_5- wherein R_5 is hydrogen, methyl, formyl or acetyl; in free form and, where such forms exist, in salt form. They can be obtained by a process comprising epoxide ring opening, appropriate substitution and/or deprotection or saponification. They have antiviral activity, particularly HIV-1 proteinase inhibiting activity, and are thus indicated for use in the treatment of retroviral diseases.

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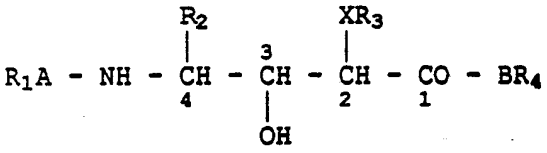
4-AMINO-3-HYDROXYCARBOXYLIC ACID DERIVATIVES

The invention relates to 4-amino-3-hydroxycarboxylic acid derivatives. It concerns the compounds of formula I



I

wherein

A and B independently are a bond or an optionally substituted aminoacyl moiety;

R_1 is hydrogen; an amino protecting group; or a group of formula R_6Y- wherein

R_6 is hydrogen or an optionally substituted alkyl, alkenyl, alkinyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl group; and

Y is -CO-; -NHCO-; -NHCS-; $-SO_2-$; -O-CO-; or -O-CS-;

R_2 is the side chain of a natural amino acid; an alkyl, arylalkyl, heteroarylalkyl or cycloalkylalkyl group; or trimethylsilylmethyl, 2-thienylmethyl or styrylmethyl;

R_3 is an optionally substituted alkyl, alkenyl, alkinyl, cycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl group;

R_4 is a group of formula $-OR_7$ or $-NHR_7$ wherein

R_7 has the significance indicated above for R_6; and

X is -S- or $-NR_5-$ wherein

R_5 is hydrogen, methyl, formyl or acetyl;

in free form and, where such forms exist, in salt form, hereinafter briefly named "a compound of the invention".

To date, there is a definite need for finding compounds which effectively inhibit retroviruses in a human infected by such a virus, and thus treat or prevent diseases caused thereby, such as acquired immunodeficiency syndrome (AIDS).

One approach for effecting retroviral inhibition is the use of an inhibitor of a viral proteinase essential for processing viral polypeptide precursors by proteolytic maturation, e.g. the HIV proteinase.

The compounds of the present invention are antivirally active. They inhibit the HIV proteinase.

R_1 preferably is 2-pyridylmethoxycarbonyl, benzyl-CH(OH)-carbonyl, phenoxymethylcarbonyl or an amino protecting group such as tert-butoxycarbonyl or benzyloxycarbonyl; it especially is benzyloxycarbonyl.

A preferably is an optionally substituted aminoacyl moiety, preferably an optionally substituted α-aminoacyl moiety such as alanine, leucine, isoleucine, asparagine, valine, tert-butylglycine, tert-leucine or histidine. It preferably is the optionally protected moiety of a natural α-amino acid, preferably of an amino acid which is a normal constitutive part of proteins. It especially is L-valine.

R_2 preferably is the side chain of a natural amino acid, preferably of an α-amino acid, preferably of an amino acid which is a normal constitutive part of proteins. It is e.g. isopropyl, aminocarbonylmethyl, methyl, 1-methylpropyl, benzyl, 4-hydroxybenzyl or isobutyl, preferably benzyl.

B preferably is an optionally substituted aminoacyl moiety, preferably an optionally substituted α-aminoacyl moiety, such as phenylalanine, valine, leucine, isoleucine, alanine or asparagine. It preferably is the optionally substituted moiety of a natural α-amino acid, preferably of an amino acid which is a normal constitutive part of proteins. It especially is L-valine.

R_4 preferably is a group $-NHR_7$; it preferably is isopropylamino, tert-butylamino, 1- or 2-naphthylmethylamino, or 2-, 3- or 4-pyridylmethylamino; it especially is benzylamino or benzimidazolylmethylamino, particularly benzimidazol-2-ylmethylamino.

R_3 preferably is an optionally substituted arylalkyl group, especially benzyl. The aryl part of arylalkyl optionally is substituted by, preferably, alkoxy or 1 to 4 carbon atoms, such as methoxy, or halogen of atomic number of from 9 to 35, such as bromine; it preferably is monosubstituted, preferably in 3 or 4 position; it especially is monosubstituted in 3 or 4 position by methoxy.

X preferably is a group $-NR_5-$ as defined above. It especially is the imino group.

R_6 preferably is an optionally substituted alkyl, arylalkyl or heteroarylalkyl group, especially alkyl; when it is optionally substituted heteroarylalkyl it preferably is pyridylalkyl, especially 2-pyridylmethyl; when it is optionally substituted arylalkyl it preferably is benzyl-CH(OH)-; when it is substituted alkyl it preferably is phenoxymethyl.

Y preferably is -CO- or -O-CO-, especially -CO-.

R_7 preferably is an optionally substituted alkyl, arylalkyl or heteroarylalkyl group, preferably phenylalkyl of altogether 7 to 10 carbon atoms such as benzyl, or a pyridylalkyl, indolylalkyl or benzimidazolylalkyl group of 1 to 4 carbon in the alkylene part; it

preferably is benzyl, 2-, 3- or 4-pyridylmethyl or benzimidazolylmethyl, especially benzyl or benzimidazolylmethyl, particularly benzimidazol-2-ylmethyl.

R_5 preferably is hydrogen or methyl, especially hydrogen.

A salt is e.g. an acid addition salt such as a hydrochloride.

The compounds of formula I normally have several chiral centers and can therefore exist in a variety of stereoisomers. The invention provides all stereoisomers as well as racemic mixtures. The isomers may be resolved or separated by conventional techniques, e.g. chromatographically.

The carbon atom in 4 position preferably has the S configuration.

An optionally substituted aminoacyl moiety preferably is unsubstituted. When it is substituted it e.g. is substituted by alkyl of 1 to 4 carbon atoms, such as in O-tert-butyl-L-serinoyl or in 2-aminobutanoyl. It preferably is in the L optically active form. It preferably is an α-aminoacyl moiety, such as valine or tert-leucine.

Optionally substituted alkyl preferably is alkyl of 1 to 5 carbon atoms, preferably of 1 to 4 carbon atoms, e.g. methyl, ethyl, isopropyl or tert-butyl; it is especially of 1 or 4 carbon atoms. The substituent is e.g. phenoxy, hydroxy or optionally protected amino.

Optionally substituted arylalkyl is e.g. phenylalkyl of altogether 7 to 10 carbon atoms, such as benzyl or 2-phenylethyl; it is optionally substituted by e.g. hydroxy, such as in benzyl-CH(OH)- or phenyl-CH(CH_2OH)-, or is e.g. naphthylalkyl of 1 to 4 carbon atoms in the alkylene part.

An amino protecting group preferably is benzyloxycarbonyl or tert-butoxycarbonyl.

Optionally substituted heteroarylalkyl preferably is pyridylalkyl, especially 2-pyridylmethyl.

Aryl, heteroaryl and the aryl parts of arylalkyl or heteroarylalkyl may be mono- or polycyclic, such as e.g. pyridyl, naphthyl, 9-fluorenylmethoxycarbonyl (FMOC) or benzimidazolyl. The alkylene part of

arylalkyl or heteroarylalkyl may be substituted by e.g. hydroxy.

A heterocyclyl group and the heterocyclyl part of a heterocyclylalkyl group is a saturated heterocyclic group having one or more heteroatoms selected from nitrogen, oxygen and sulfur. It preferably has 5 or 6 ring constitutent atoms, and preferably up to 3 heteroatoms.

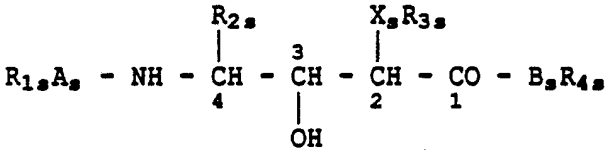
Cycloalkylalkyl preferably is cyclohexylalkyl; it preferably is of 1 to 4 carbon atoms in the alkylene part.

A subgroup of compounds of formula I is the compounds of formula I wherein A and B independently are a bond, the aminoacyl moiety of a natural amino acid, the D-enantiomer thereof, or tert-butylglycine, and the other substituents are as defined above.

A further subgroup is the compounds of formula I wherein R_1A- is an optionally substituted and optionally N-terminal protected natural aminoacyl moiety, -BR_4 is a natural aminoacyl moiety optionally esterified or amidated at the C-terminus , R_2 is the side chain of a natural amino acid, R_3 is an alkyl, alkenyl, cycloalkyl, aryl or arylalkyl group such as naphthylmethyl and X is as defined above.

A further subgroup is the compounds of formula I wherein R_1 is benzylyoxycarbonyl, 2-pyridylmethoxycarbonyl, phenyllactoyl or phenoxymethylcarbonyl, A is L-valine or L-tert-leucine, R_2 is benzyl, X is -NH-, R_3 is benzyl, 3- or 4-methoxybenzyl or 4-bromobenzyl, B is L-valine and R_4 is benzylamino or benzimidazol-2-ylmethylamino, and the carbon atom in 4 position has the S configuration.

A further subgroup is the compounds of formula Is



Is

wherein

R_{1s} is hydrogen; phenylalkyloxycarbonyl of altogether 8 to 10 carbon atoms; alkyloxycarbonyl of altogether 2 to 10 carbon atoms; quinolylcarbonyl or quinolylsulfonyl; pyridylmethoxycarbonyl; aminocaproyl optionally protected by tert-butoxycarbonyl; 9-fluorenylmethoxycarbonyl (FMOC); phenyllactoyl; isovalerianoyl; phenoxymethylcarbonyl; palmitoyl; or 4-hydroxyphenylpropionyl;

A_s is a bond; a natural α-aminoacyl moiety; the corresponding D optical isomer form; L- or D-tert-leucine; O-tert-butyl-L-serine; or L-2-aminobutanoyl;

R_{2s} is alkyl of 3 or 4 carbon atoms or phenylalkyl of altogether 7 to 9 carbon atoms;

X_s is -S- or $-NR_{5s}-$ wherein R_{5s} is hydrogen or methyl;

R_{3s} is alkyl of 3 to 5 carbon atoms; cycloalkyl of 5 to 7 carbon atoms optionally monosubstituted by hydroxy; phenyl; phenylalkyl of altogether 7 to 9 carbon atoms optionally monosubstituted in the phenyl ring by hydroxy, alkoxy of 1 to 3 carbon atoms, halogen of atomic number of from 9 to 35, or phenyl; a pyridylalkyl, indolylalkyl or naphthylalkyl group of 1 to 3 carbon atoms in the alkylene part; or phenylalkenyl of 2 to 4 carbon atoms in the alkenylene part;

B_s is a bond; a natural α-aminoacyl moiety; the corresponding D optical isomer form; L- or D-tert-leucine; or aminocyclopropan-1-carbonyl;

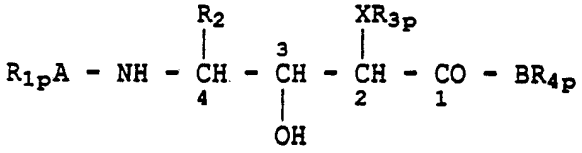
R_{4s} is hydroxy; an alkoxy or alkylamino group of 1 to 5 carbon atoms; phenylalkylamino of altogether 7 to 9 carbon atoms optionally monosubstituted in the phenyl ring or in the alkylene part by hydroxy, or monosubstituted in the phenyl ring by halogen of atomic number of from 9 to 35; benzimidazolylalkoxy or benzimidazolylalkylamino of 1 to 3 carbon atoms in the alkylene part optionally mono- or disubstituted in the aryl part by halogen of atomic number of from 9 to 35 or nitro; or an indolylalkylamino, pyridylalkylamino or morpholinylalkylamino moiety of 1 to 3 carbon atoms in the alkylene part; and

the configuration in 4 position is S,

in free form and, where such forms exist, in salt form.

In a subgroup of compounds of formula Is, when A_s or B_s is a natural α-aminoacyl moiety it is valine, tryptophane, phenylalanine, asparagine, isoleucine, glutamine, leucine, alanine or histidine; in a further subgroup, when R_{1s} is phenylalkyloxycarbonyl it is benzyloxycarbonyl.

A further subgroup is the compounds of formula Ip_1



Ip_1

wherein

A, B, R_2 and X are as defined above;

R_{1p} with the exception of hydrogen has the significance indicated above for R_1;

R_{3p} with the exception of optionally substituted cycloalkyl has the significance indicated above for R_3; and

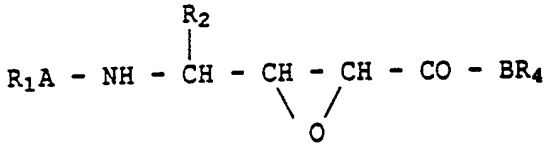
R_{4p} is hydroxy or a group of formula $-OR_7$ or $-NHR_7$ as defined above;

in free form and, where such forms exist, in salt form.

A further subgroup is the compounds Ip_2, i.e. the compounds of formula I as defined above with the exception that R_4 is hydroxy or a group of formula $-OR_7$ or $-NHR_7$ as defined above.

The compounds of the invention may be prepared by a process which comprises

a) submitting an epoxide of formula II



II

wherein the substituents are as defined above,

to **ring opening** in the presence of a compound of formula III

III

wherein the substituents are as defined above, where indicated in a further reactive form; or

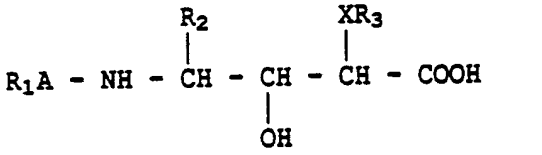
b) for the preparation of the compounds of formula I wherein

$-BR_4$ is other than hydroxy [b_1], or

R_1 is other than hydrogen or HY- [b_2],

appropriately **substituting** a corresponding compound of formula I wherein $-CO-BR_4$ is carboxy or R_1 is hydrogen or HY-, e.g.

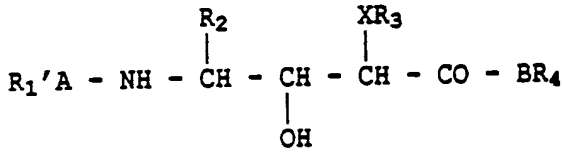
b_1) substituting a corresponding compound of formula Ia



Ia

wherein the substituents are as defined above, or

b_2) substituting a corresponding compound of formula Ib



Ib

wherein R_1' is hydrogen or HY- and

the other substituents are as defined above;

and where indicated **deprotecting or saponifying** a resultant compound of formula I in protected or esterified form,

and recovering the resultant compounds of formula I in free form or, where such forms exist, in salt form.

The process of the invention can be carried out in conventional manner.

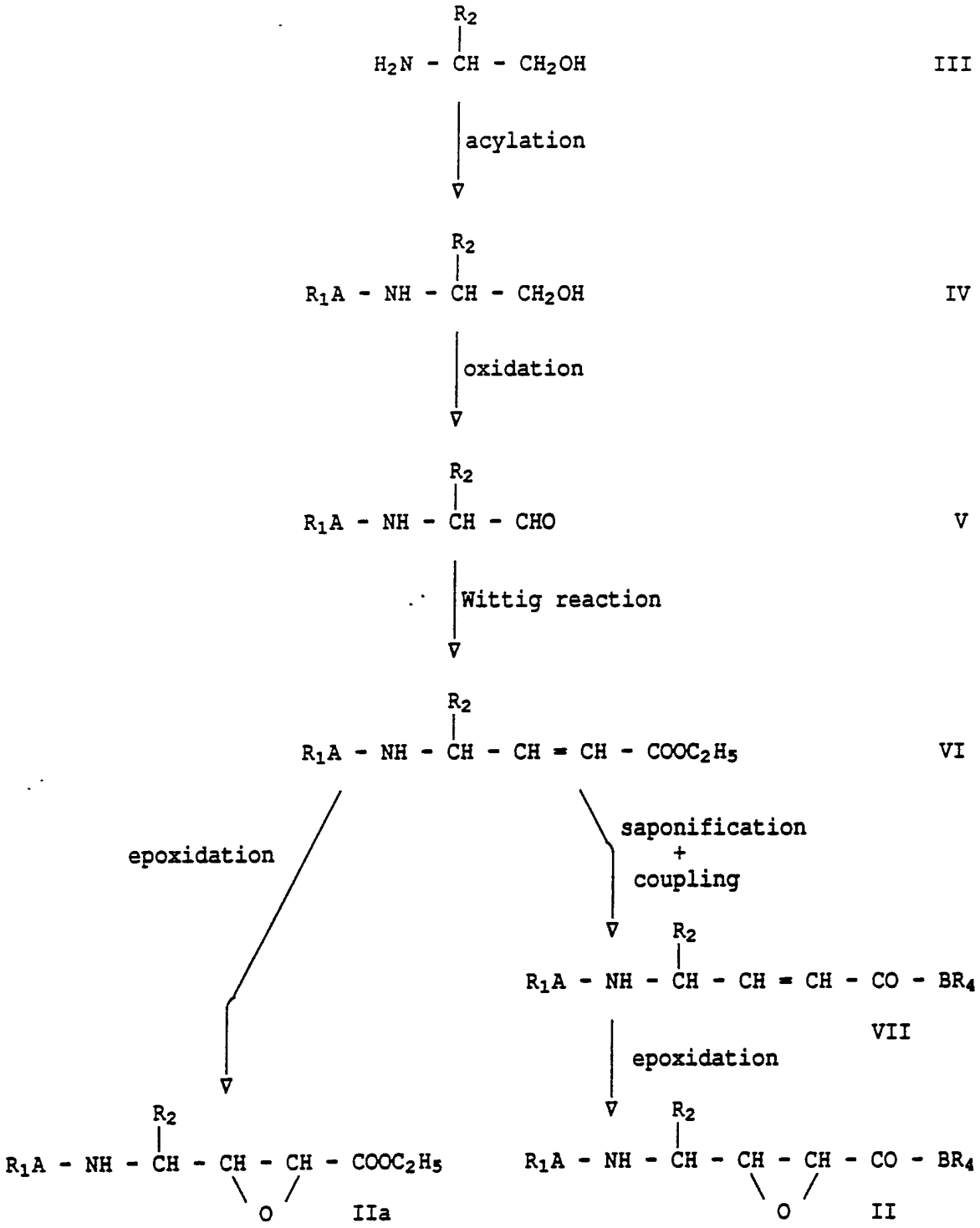
Process variant a) is effected e.g. in an inert solvent such as an ether, e.g. tetrahydrofuran, or acetonitrile. The temperature preferably is between about -50°C and the boiling temperature of the reaction mixture, preferably between about -20°C and about 80°C. The compound of formula III is an appropriate amine or mercaptan. A further reactive form preferably is a salt of a mercaptan, e.g. an alkali metal salt such as the potassium salt.

Process variant b) is effected using conditions known for coupling amino acids. The reaction preferably is effected in an inert solvent, such as an amide, e.g. dimethylformamide, or an ether, e.g. tetrahydrofuran. The temperature preferably is between about room temperature and the boiling temperature of the reaction mixture, preferably about room temperature.

Deprotection conveniently is effected by hydrolysis, preferably under acidic conditions for removing e.g. a hydroxy or amino protecting group such as tert-butoxycarbonyl, preferably with trifluoroacetic acid, or hydrogenolytically for removing e.g. benzyloxycarbonyl. **Saponification** is effected preferably with aqueous sodium hydroxide solution for removing e.g. alkoxy. The temperature preferably is between about -20°C and about 60°C, it conveniently is about room temperature. An organic solvent such as dichloromethane or tetrahydrofuran conveniently is used.

The resultant compounds of formula I can be isolated from the reaction mixture and purified according to known methods, e.g. chromatographically.

The compounds of formula II can be prepared e.g. in accordance with the following reaction scheme:



In the above reaction scheme the substituents are as defined above. The single reaction steps may be carried out according to reaction conditions conventionally employed in such reactions, whereby the various intermediates can, where appropriate, be reacted further without isolation.

Insofar as they are not particularly described above or in the Examples, the starting materials and intermediates are either known or can be prepared according to known methods or analogously to known methods or methods described in the Examples.

The following Examples illustrate the invention. The carbon atom in the 4 position in formula I has the **S configuration**. All temperatures are in degrees Centigrade. The abbreviations for amino acids follow the international (IUPAC) rules. All NMR spectra are in $CDCl_3$ unless indicated otherwise; the shifts are in ppm relative to trimethylsilane.

Other abbreviations have the following meaning:

BOC = tert-butoxycarbonyl;
Bu = n-butyl;
Bz = benzyl;

ch = hydrochloride;
cHex = cyclohexyl;

d. = decomposition;
dch = dihydrochloride;
depr. = deprotection;

Et = ethyl;
Ex. = Example;

FMOC = 9-fluorenylmethoxycarbonyl;

iBu = isobutyl = 2-methylpropyl;
iPr = isopropyl;

Me = methyl;
m.p. = melting point;

OEt = ethoxy;
OMe = methoxy;

Ph = phenyl;
Phe = a phenylalanine moiety;
Pr = n-propyl;

s. = sublimation;
sap. = saponification;
Su = the N-hydroxysuccinimide ester moiety;

tBu = tert-butyl;
tch = trihydrochloride;
tLeu = a tert-leucine moiety $-NHCH[-C(CH_3)_3]CO-$;

Z = benzyloxycarbonyl.

Example 1: 2-Benzylamino-4(S)-[(N-benzyloxycarbonyl-L-valinoyl)amino]-3-hydroxy-5-phenylpentanoic acid ethyl ester

[Formula I: R_1 = Z; A = L-Val; R_2, R_3 = Bz; X = -NH-; B = a bond; R_4 = OEt]

[Process variant a), ring opening]

400 mg of **4(S)-[(N-benzyloxycarbonyl-L-valinoyl)amino]-2,3-epoxy-5-phenylpentanoic acid ethyl ester** (an intermediate of formula II; compound A hereafter) are dissolved in 6 ml of tetrahydrofuran. 185 µl of **benzylamine** (an intermediate of formula III) are added and the solution is kept at 60° for 2 days. The solvent is evaporated and the residue chromatographed on silicagel (solvent: toluene/ethyl acetate 2:1). The **title compound** is obtained (m.p. 52-55°).

Example 1a: 4(S)-[(N-tert-Butoxycarbonyl-L-valinoyl)amino]-2-benzylthio-3-hydroxy-5-phenylpentanoic acid ethyl ester

[Formula I: R_1 = BOC; A = L-Val; R_2,R_3 = Bz; X = -S-; B = a bond; R_4 =OEt]

[Process variant a), ring opening]

1.15 g of **benzylmercaptan** (an intermediate of formula III) **potassium salt** are dissolved in 20 ml of acetonitrile and cooled to -50°. 2 g of **4(S)-[(N-tert-butoxycarbonyl-L-valinoyl)amino]-2,3-epoxy-5-phenylpentanoic acid ethyl ester** (an intermediate of formula II; compound C hereafter) dissolved in 10 ml of acetonitrile are added and the mixture is kept at -20° for 48 hours. After neutralization with acetic acid the mixture is filtered, the solvent evaporated and the residue chromatographed on silicagel (solvent: toluene/ethyl acetate 4:1). The **title compound** is obtained (sirup):

^{1}H-NMR: 1.27 (t,3H); 1.42 (s,9H); 2.67-3.15 (AB,2H); 3.24 (d,1H); 3.47 (d,1H); 3.70 (AB,2H); 3.84 (dd,1H); 4.17 (q,2H); 4.22 (q,1H); 4.78 (q,1H); 7.15-7.40 (m,10H);

Example 2: N-{[2-Benzylamino-4(S)-[(N-benzyloxycarbonyl-L-valinoyl)amino]-3-hydroxy-5-phenyl]pentanoyl}-L-valine benzylamide

[Formula I: R_1 = Z; A,B = L-Val; R_2,R_3 = Bz; X = -NH-; R_4 = NHBz]

[Process variant b_1), substitution]

230 mg of **compound of Example 4a** are dissolved in 5 ml of dimethylformamide. 87 mg of **L-valine benzylamide** (an intermediate of formula H-BR_4), 57 mg of hydroxybenzotriazole and 104 mg of dicyclohexylcarbodiimide are added at room temperature. After 24 hours stirring at room temperature the solution is filtered, the solvent evaporated and the residue chromatographed on silicagel (solvent: gradient toluene/ethyl acetate 1:1 to 1:3). The **title compound** is obtained (amorphous; m.p. 81-84°).

Example 2a: N-{[2-Benzylamino-4(S)-[(N-benzyloxycarbonyl-L-valinoyl)-amino]-3-hydroxy-5-phenyl]pentanoyl}-L-leucine benzylamide

[Formula I: R_1 = Z; A = L-Val; R_2,R_3 = Bz; X = -NH-; B = L-Leu; R_4 = NHBz]

[Process variant b_1), substitution]

220 mg of **compound of Example 4a** in 10 ml of a mixture of dry tetrahydrofuran and dimethylformamide (1:1) are protected from light and stirred at room temperature in the presence of 195 mg of 1-benzotriazolyl-oxy-tris-(dimethylamino)phosphonium hexafluorophosphate and 49 µl of N-methylmorpholine for 15 minutes. 106 mg of **L-leucine benzylamide** (an intermediate of formula H-BR_4) are then added and the reaction mixture is stirred at room temperature overnight. The solvent is removed, water is added and the crude product extracted with ethyl acetate. The organic layers are dried, the solvent evaporated and the residue chromatographed on silicagel (solvent: gradient toluene/ethyl acetate 3:2 to 1:1). The **title compound** is obtained (m.p. 190-201°).

Example 3: N-{[Benzylamino-4(S)-[(N-benzyloxycarbonyl-O-tert-butyl-L-serinoyl)amino]-3-hydroxy-5-phenyl]pentanoyl}-L-valine benzylamide

[Formula I: R_1 = Z; A = O-tBu-L-Ser; R_2,R_3 = Bz; X = -NH-; B = L-Val; R_4 = NHBz]

[Process variant b_2), substitution]

0.35 g of **N-benzyloxycarbonyl-O-tert-butyl-L-serine-N-hydroxy-succinimide ester** (an intermediate of formula R_1A-Q wherein Q is N-hydroxysuccinimidyloxy) are added to a solution of 0.1 g of **compound of Example 119** in 4 ml of dioxane. The mixture is stirred for 6 days at room temperature, the solvent is evaporated and the residue is chromatographed on silicagel (solvent: cyclohexane/ethyl acetate 1:1). The **title compound** is obtained (m.p. 59-63°).

Example 3a: N-{[2-Benzylamino-4(S)-[(N-benzyloxycarbonyl-L-valinoyl)amino]-3-hydroxy-6-methyl]heptanoyl}-L-phenylalanine methylester

[Formula I: R_1 = Z; A = L-Val; R_2 = iBu; X = -NH-; R_3 = Bz; B = L-Phe; R_4 = OMe]

[Process variant b_2), substitution]

96 mg of **compound of Example 118** are dissolved in 2 ml of tetrahydrofuran. 82 mg of **N-benzyloxycarbonyl-L-valine-p-nitrophenyl ester** (an intermediate of formula R_1A-Q wherein Q is p-nitrophenyloxy) and 200 mg of K_2CO_3 are added and the reaction mixture is stirred for 3 days. The solution is filtered and the solvent evaporated. The residue is dissolved in ethyl acetate; the solution is washed with aqueous 0.1 N HCl, saturated $NaHCO_3$ solution, dried and the solvent evaporated. The residue is chromatographed on silicagel (solvent: toluene/ethyl acetate 1:1), the **title compound** obtained (oil):

^{1}H-NMR: 0.90-1.00 (2d,12H); 1.20-1.40 (m,1H); 1.50-1.80 (m,2H); 2.20 (oct,1H); 3.05-3.20 (m,3H); 3.55 (bs,1H); 3.75 (s,3H); 3.84 (d,1H); 3.97 (dd,1H); 4.08-4.17 (m,1H); 4.90 (dd,1H); 5.08-5.20 (m,2H); 6.60 (d,1H); 7.10-7.38 (m,15H); 8.10 (d,1H);

Example 3b: N-{[2-Benzylamino-4(S)-[(N-benzyloxycarbonyl-L-histidinoyl)-amino]-3-hydroxy-5-phenyl]pentanoyl}-L-valine benzylamide

[Formula I: R_1 = Z; A = L-His; R_2,R_3 = Bz; X = -NH-; B = L-Val; R_4 = NHBz]

[Process variant b_2), substitution]

300 mg of **N-benzyloxycarbonyl-L-histidinoyl hydrazide** (an intermediate of formula R_1A-Q wherein Q is $-NHNH_2$) are added at 5° to 4 ml of 1 N HCl solution. A solution of 80 mg of sodium nitrite in 2 ml of water is added at 5°, the mixture is stirred for 5 minutes and quenched with 8 ml of saturated Na_2CO_3 solution. The resulting white solid is washed twice with water, dissolved in 4 ml of dimethylformamide and added to a solution of 150 mg of **compound of Example 119** in 3 ml of dimethylformamide. The mixture is stirred for 6 hours at room temperature, the solvent is evaporated and the residue is chromatographed on silicagel (solvent: ethyl acetate). The **title compound** is obtained (resin):

^{1}H-NMR (DMSO): 0.88 and 0.89 (2d,J=6Hz,6H); 2.04 (oct,J=6Hz,1H); 2.61-2.68 (m,1H); 2.73-2.90 (m,3H); 3.42-3.56 (m,3H); 4.22-4.38 (m,5H); 5.03 (s,2H); 5.13 (b,1H); 6.72 (s,1H); 7.10-7.35 (m,20H); 7.39 (d,J=9Hz,1H); 7.48 (s,1H); 7.65 (d,J=9Hz,1H); 8.26 (t, J=6Hz,1H);

Example 3c: N-{[2-Benzylamino-3-hydroxy-5-phenyl-4(S)-[(N-2-quinolyl-carbonyl-L-asparaginoyl)amino]]pentanoyl}-L-valine benzylamide

[Formula I: R_1 = quinolin-2-ylcarbonyl; A = L-Asn; R_2,R_3 = Bz; X = -NH-; B = L-Val; R_4 = NHBz]

[Process variant b_2), substitution]

55 mg of diphenylphosphoryl azide and 20 mg of N-methylmorpholine are added to a solution of 100 mg of **compound of Example 119** and 57 mg of **N-(2-quinolylcarbonyl)-L-asparagine** (an intermediate of formula R_1A-Q wherein Q is -OH) in 3 ml of dimethylformamide. The mixture is stirred for 2 days at room temperature, the solvent is evaporated and the residue is chromatographedon silicagel. The **title compound** is obtained:

^{1}H-NMR: 0.92 and 0.95 (2d,6H); 1.70 (b,1H); 2.16-2.24 (m,1H); 2.82 (dd,2H); 2.92 and 3.01 (ABX,2H); 3.34 (d,1H); 3.57 and 3.66 (AB,2H); 3.86-3.90 (m,1H); 4.26 (dd,1H); 4.31-4.46 (m,3H); 4.89-4.95 (m,1H); 6.68-6.72 (m,1H); 6.95-7.00 (m,1H); 7.09-7.30 (m,17H); 7.65-7.68 (m,1H); 7.79-7.82 (m,1H); 7.86-7.93 (m,2H); 8.16-8.21 (m,2H); 8.31 (d,1H); 8.73 (d,1H);

Example 4: N-[2-Benzylamino-4(S)-(N-benzyloxycarbonyl-L-serinoyl)amino-3-hydroxy-5-phenylpentanoyl]-L-valine benzylamide

[Formula I: R_1 = Z; A = L-Ser; R_2,R_3 = Bz; X = -NH-; B = L-Val; R_4 = NHBz]

[Deprotection]

2 ml of **trifluoroacetic acid** are added to a solution of 55 mg of **compound of Example 3** in 2 ml of dichloromethane. The mixture is stirred for 16 hours at room temperature, the solvent is evaporated, toluene is added and evaporated (twice), the residue is solved in dichloromethane, washed with 0.1 N NaOH, dried over $MgSO_4$, concentrated in vacuo and chromatographed on silicagel (solvent: cyclohexane/ethyl acetate 1:2). The **title compound** is obtained (m.p. 76-81°).

Example 4a: [2-Benzylamino-4(S)-(N-benzyloxycarbonyl-L-valinoyl)amino]-3-hydroxy-5-phenylpentanoic acid

[Formula I: R_1 = Z; A = L-Val; R_2,R_3 = Bz; X = -NH-; B = a bond; R_4 = OH]

[Saponification]

330 mg of **compound of Example 1** are dissolved in 3 ml of tetrahydrofuran. 627 µl of 1N aqueous **sodium hydroxide** solution are added and the reaction mixture is stirred for 10 hours at room temperature. Neutralization with dilute aqueous HCl solution leads to a white precipitate which is filtered off and dried. The **title compound** is obtained (m.p. 187-193°).

The following further compounds of the invention (formula I) are obtained in analogous manner:

Ex. No.	R_1	A	R_2	X	R_3	B	R_4	Process variant	m.p.
5	Z	L-Val	Bz	-NH-	Bz	L-Val	5,6-diCl-benzimid-azol-2-ylmethoxy	a) b)	90-95°
6	Z	L-Val	Bz	-NH-	Bz	L-Val	benzimidazol-2-ylmethoxy	a) b)	86-90°
7	Z	L-Val	Bz	-NH-	Bz	L-Val	OMe	a) b)	118-120°
8	Z	L-Val	Bz	-NH-	Bz	L-Val	2-(indol-3-yl)-ethylamino	a) b)	106-114°
9	Z	L-Val	Bz	-NH-	Bz	L-Ile	NHBz	a) b)	145-166°
10	Z	L-Val	Bz	-NH-	Bz	L-Asn	NHBz	a) b)	208-214°
11	Z	L-Val	Bz	-NH-	Bz	L-Val	2-pyridyl-methylamino	a) b)	129-136° ch 115°d. dch 134-137°
12	Z	L-Try	Bz	-NH-	Bz	L-Val	NHBz	a) b)	79-84°
13	Z	L-Asn	Bz	-NH-	Bz	L-Val	NHBz	a) b)	185-193° ch 135-137°
14	Z	L-Ile	Bz	-NH-	Bz	L-Val	NHBz	a) b)	175-180°
15	Z	L-2-amino-butanoyl	Bz	-NH-	Bz	L-Val	NHBz	a) b)	153-157°
16	Z	D-Val	Bz	-NH-	Bz	L-Val	NHBz	a) b)	134-138°
17	BOC	L-Val	Bz	-NH-	Bz	L-Val	NHBz	a) b)	126-129°
18	Z	L-Gln	Bz	-NH-	Bz	L-Val	NHBz	a) b)	178-189°
19	Z	L-Val	Bz	-NH-	phenyl	L-Val	NHBz	a) b)	120-130°
20	Z	L-Val	Bz	-NH-	cHex	L-Val	NHBz	a) b)	85-95°
21	Z	L-Val	Bz	-NH-	Bu	L-Val	NHBz	a) b)	149-155°
22	Z	L-Leu	Bz	-NH-	Bz	L-Val	NHBz	a) b)	157-161°

Ex. No.	R_1	A	R_2	X	R_3	B	R_4	Process variant	m.p.
23	Z	L-Ala	Bz	-NH-	Bz	L-Val	NHBz	a) b)	98-103°
24	Z	L-Val	Bz	-NH-	2-phenylethyl	L-Val	NHBz	a) b)	127-130°
25	Z	L-Val	Bz	-NH-	2-(indol-2-yl)-ethyl	L-Val	NHBz	a) b)	sirup;NMR[h)]
26	Z	L-Val	Bz	-NH-	1-naphthyl-methyl	L-Val	NHBz	a) b)	162-170°
27	Z	L-Val	Bz	-NH-	3-pyridyl-methyl	L-Val	NHBz	a) b)	79-84°
28	Z	L-Val	Bz	-NH-	2-(2-pyridyl)-ethyl	L-Val	NHBz	a) b)	59-66°
29	Z	L-Val	Bz	-NH-	4-MeO-Bz	L-Val	NHBz	a) b)	72-80°
30	Z	L-Val	Bz	-NH-	4-Cl-Bz	L-Val	NHBz	a) b)	79-82°
31	Z	L-Val	Bz	-S-	Bz	L-Val	NHBz	a) b)	oil; NMR[h)]
32	2-quinolyl-carbonyl	L-Val	Bz	-NH-	Bz	L-Val	2-pyridyl-methylamino	a) b)	oil; NMR[h)]
33	Z	L-Val	Bz	-NH-	Bz	L-Val	OEt	a) b)	114-130°
34	Z	L-Val	Bz	-NH-	Bz	L-Val	NHtBu	a) b)	159-168°
35	2-quinolyl-carbonyl	L-Val	Bz	-NH-	Bz	L-Val	NHBz	a) b)	83-86°
36	2-pyridyl-methoxycarbonyl	L-Val	Bz	-NH-	Bz	L-Val	NHBz	a) b)	oil; NMR[h)]
37	Z	L-tLeu	Bz	-NH-	Bz	L-Val	NHBz	a) b)	78-82°;NMR[h)] ch 128-131°
38	2-quinolyl-carbonyl	L-Val	Bz	-NH-	Bz	bond	OEt	a) b)	oil; NMR[h)]
39	BOC	bond	Bz	-S-	Bz	L-Val	NHBz	a) b)	55-62°
40[f)]	Z	L-Val	Bz	-NH-	Bz	L-Val	3-pyridyl-methylamino	a) b)	a NMR[h)]; b 77-82°;NMR[h)]

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Ex. No.	R_1	A	R_2	X	R_3	B	R_4	Process variant	m.p.
41	Z	L-Val	Bz	-NH-	Bz	L-Val	4-pyridyl-methylamino	a) b)	148-152°
42[e]	Z	L-Val	Bz	-NH-	Bz	L- or D-tLeu	NHBz	a) b)	a 83-87°;NMR[h] b 82-86°;NMR[h]
43	BOC	bond	Bz	-NH-	Bz	L-Val	3-pyridyl-methylamino	a) b)	oil; NMR[h]
44	BOC	bond	Bz	-NH-	Bz	L-Val	2-pyridyl-methylamino	a) b)	oil; NMR[h]
45	BOC	bond	Bz	-NH-	Bz	L-Val	4-pyridyl-methylamino	a) b)	oil; NMR[h]
46[g]	BOC	bond	Bz	-NH-	Bz	L- and D-tLeu	NHBz	a) b)	oil; NMR[h]
47	octyloxy-carbonyl	L-tLeu	Bz	-NH-	Bz	L-Val	NHBz	a) b)	67-70°
48	BOC	bond	Bz	-NH-	4-Cl-Bz	L-Val	benzimidazol-2-ylmethylamino	a) b)	111-115°
49	FMOC	L-tLeu	Bz	-NH-	Bz	L-Val	NHBz	a) b)	84-89°
50	BOC-NH(CH_2)$_5$CO-L-Val		Bz	-NH-	Bz	L-Val	NHBz	a) b)	128-133°
51	D-BzCH(OH)CO-L-tLeu		Bz	-NH-	Bz	L-Val	NHBz	a) b)	125-134°;NMR[h]
52	BOC	L-tLeu	Bz	-NH-	Bz	L-Val	NHBz	a) b)	80-85°
53	L-iPrCH(OH)CO-	bond	Bz	-NH-	Bz	L-Val	NHBz	a) b)	white resin; NMR[h]
54	Z	L-Val	Bz	-NH-	2-(4-OH-phenyl)-ethyl	L-Val	NHBz	a) b)	83-89°
55	Z	L-Val	Bz	-NMe-	3-phenylprop-2(E)-enyl	L-Val	NHBz	a) b)	63-73°
56	Z	L-Val	Bz	-NH-	3-MeO-Bz	L-Val	benzimidazol-2-ylmethylamino	a) b)	198-204°;NMR[h]

Ex. No.	R_1	A	R_2	X	R_3	B	R_4	Process variant	m.p.
57	Z	L-Val	Bz	-NH-	3-MeO-Bz	L-Val	NHBz	a) b)	83-86°
58	Z	L-Val	Bz	-NH-	4-Cl-Bz	L-Val	2-pyridyl-methylamino	a) b)	143-151°
59	Z	L-Val	Bz	-NH-	4-MeO-Bz	L-Val	benzimidazol-2-ylmethylamino	a) b)	205-209°;NMR[h)]
60	Z	L-Val	2-Ph-ethyl	-NH-	4-Cl-Bz	L-Val	NHBz	a) b)	82-85°
61	Z	L-Val	2-Ph-ethyl	-NH-	4-Cl-Bz	L-Val	benzimidazol-2-ylmethylamino	a) b)	100-107°
62	Z	L-Val	Bz	-NH-	biphenyl	L-Val	benzimidazol-2-ylmethylamino	a) b)	124-130°
63	Z	L-Val	Bz	-NH-	biphenyl	L-Val	NHBz	a) b)	168-175°
64	Z	L-Val	Bz	-NH-	Bz	-NHC(-CH_2CH_2-)CO-	NHBz	a) b)	77-82°
65	Z	L-Val	Bz	-NH-	4-Br-Bz	L-Val	NHBz	a) b)	84-87°
66	Z	L-Val	Bz	-NH-	Bz	L-Val	benzimidazol-2-ylmethylamino	a) b)	201-204°;NMR[h)]
67	Z	L-Val	Bz	-NH-	4-Br-Bz	L-Val	benzimidazol-2-ylmethylamino	a) b)	204-208°;NMR[h)]
68	Z	L-Val	Bz	-NH-	Bz	L-Val	4-Br-benzylamino	a) b)	155-161°
69	2-pyridyl-methoxycarbonyl	L-Val	Bz	-NH-	Bz	L-Val	2-pyridyl-methylamino	a) b)	79-80°
70	Z	L-Val	Bz	-NH-	Bz	bond	NHBz	a) b)	50-55°
71	Z	L-Asn	Bz	-NH-	Bz	bond	NHBz	a) b)	145-155°
72	BOC	bond	Bz	-NH-	Bz	bond	NHBz	a)	50-53°
73	Z	bond	Bz	-NH-	Bz	bond	NHBz	a)	oil; NMR[h)]
74	BOC	bond	iBu	-NH-	Bz	L-Phe	OMe	a) b)	oil; NMR[h)]
75	BOC	bond	Bz	-NH-	Bz	L-Val	NHBz	a) b)	154-163°
76	BOC	bond	iBu	-NH-	Bz	bond	OEt	a)	oil; NMR[h)]

Ex. No.	R_1	A	R_2	X	R_3	B	R_4	Process variant	m.p.
77	BOC	bond	Bz	-NH-	Bz	bond	OEt	a)	sirup; NMR[h)]
78	Z	L-Val	Bz	-NH-	Ph	bond	OEt	a) b)	NMR[h)]
79	Z	L-Val	Bz	-NH-	cHex	bond	OEt	a) b)	55-65°
80	Z	L-Val	Bz	-NH-	Bu	bond	OEt	a) b)	63-67°
81	Z	L-Val	Bz	-NH-	1-naphthyl-methyl	bond	OEt	a) b)	NMR[h)]
82	Z	L-Val	Bz	-NH-	2-(indol-2-yl)-ethyl	bond	OEt	a) b)	resin; NMR[h)]
83	Z	L-Val	Bz	-NH-	3-pyridyl-methyl	bond	OEt	a) b)	resin; NMR[h)]
84	Z	L-Val	Bz	-NH-	2-(2-pyridyl-ethyl	bond	OEt	a) b)	NMR[h)]
85	Z	L-Val	Bz	-NH-	4-MeO-Bz	bond	OEt	a) b)	82-89°
86	Z	L-Val	Bz	-NH-	4-Cl-Bz	bond	OEt	a) b)	88-96°
87	Z	L-Val	Bz	-NH-	2-phenylethyl	bond	OEt	a) b)	90-96°
88	Z	L-Val	Bz	-NH-	biphenyl	bond	OEt	a) b)	66-72°
89	Z	L-Val	2-Ph-ethyl	-NH-	4-Cl-Bz	bond	OEt	a) b)	90-96°
90	Z	L-Val	Bz	-NH-	3-MeO-Bz	bond	OEt	a) b)	93-99°
91	Z	L-Val	Bz	-NMe-	3-phenylprop-2(E)-enyl	bond	OEt	a) b)	oil; NMR[h)]
92	Z	L-Val	Bz	-NH-	2-(4-OH-phenyl)-ethyl	bond	OEt	a) b)	50-57°
93	BOC	bond	Bz	-S-	Bz	bond	OEt	a)	sirup; NMR[h)]
94	2-pyridyl-methoxycarbonyl	L-Val	Bz	-NH-	Bz	bond	OEt	a) b)	

Ex. No.	R_1	A	R_2	X	R_3	B	R_4	Process variant	m.p.
95	BOC	bond	Bz	-NH-	Bz	bond	OEt	a)	
96	2-pyridyl-methoxycarbonyl	L-Val	Bz	-NH-	Bz	bond	OH	a) b) sap.	
97	Z	L-Val	Bz	-NH-	4-MeO-Bz	bond	2,2-dimethyl-propylamino	a) b)	resin; NMR[h)]
98	BOC	bond	Bz	-S-	Ph	bond	OMe	a)	oil; NMR[h)]
99	Z	L-Val	Bz	-NH-	4-MeO-Bz	L-Val	2-(4-morpholinyl)-ethylamino	a) b)	94-97°;NMR[h)]
100	Z	L-Val	Bz	-NH-	4-MeO-Bz	L-Val	2-(4-OH-phenyl)-ethylamino	a) b)	80-85°;NMR[h)]
101	Z	L-Val	Bz	-NH-	cis-4-OH-cHex	bond	OEt	a) b)	58-68°
102	Z	L-Val	Bz	-NH-	trans-4-OH-cHex	bond	OEt	a) b)	47-55°
103	Z	L-Val	Bz	-NH-	trans-4-OH-cHex	L-Val	NHBz	a) b)	86-95°
104	Z	L-Val	Bz	-NH-	cis-4-OH-cHex	L-Val	NHBz	a) b)	130-135°
105	Z	L-Val	Bz	-NH-	4-Br-Bz	bond	OEt	a) b)	93-97°
106	phenoxy-methylcarbonyl	L-tLeu	Bz	-NH-	Bz	L-Val	NHBz	a) b)	77-82°;NMR[h)]
107	H	bond	Bz	-NH-	4-Cl-Bz	L-Val	benzimidazol-2-ylmethylamino	a) b) depr.	tch 171-175°
108	palmitoyl	L-tLeu	Bz	-NH-	Bz	L-Val	NHBz	a) b)	oil; NMR[h)]
109	4-OH-Ph-propionyl	L-tLeu	Bz	-NH-	Bz	L-Val	NHBz	a) b)	101-104°
110	8-quinolyl-sulfonyl	L-tLeu	Bz	-NH-	Bz	L-Val	NHBz	a) b)	101-105°

Ex. No.	R_1	A	R_2	X	R_3	B	R_4	Process variant	m.p.
111	Z	L-Val	Bz	-NH-	Bz	L-Val	5-NO_2-benzimid-azol-2-ylmethoxy	a) b)	89-93°
112	H	bond	Bz	-NH-	Bz	L-Val	4-pyridyl-methylamino	a) b) depr.	oil
113[g)]	H	bond	Bz	-NH-	Bz	L- and D-tLeu	NHBz	a) b) depr.	oil
114	H	L-tLeu	Bz	-NH-	Bz	L-Val	NHBz	a) b) depr.	white resin; NMR[h)]
115	H	L-Val	Bz	-NH-	Bz	L-Val	NHBz	a) b) depr.	59-64°
116	H	bond	Bz	-NH-	Bz	bond	NHBz	a) depr.	NMR[h)]
117	H	L-Val	Bz	-NH-	Bz	bond	OEt	a) b) depr.	oil
118	H	bond	iBu	-NH-	Bz	L-Phe	OMe	a) b) depr.	oil; NMR[h)]
119	H	bond	Bz	-NH-	Bz	L-Val	NHBz	a) b) depr.	138-152°
120	H	bond	Bz	-S-	Bz	L-Val	NHBz	a) b) depr.	NMR[h)]
121	H	bond	Bz	-NH-	Bz	L-Val	3-pyridyl-methylamino	a) b) depr.	oil
122	H	bond	Bz	-NH-	Bz	L-Val	2-pyridyl-methylamino	a) b) depr.	oil
123	Z	L-Val	Bz	-NH-	2-(4-OH-phenyl)-ethyl	bond	OH	a) b) sap.	218-225°
124	BOC	bond	iBu	-NH-	Bz	bond	OH	a) sap.	173° (s.)
125	BOC	bond	Bz	-NH-	Bz	bond	OH	a) sap.	210-214°
126	Z	L-Val	Bz	-NH-	3-pyridyl-methyl	bond	OH	a) b) sap.	amorphous
127	Z	L-Val	Bz	-NH-	2-(2-pyridyl-ethyl	bond	OH	a) b) sap.	amorphous
128	BOC	bond	Bz	-S-	Bz	bond	OH	a) sap.	amorphous
129	Z	L-Val	Bz	-NH-	biphenyl	bond	OH	a) b) sap.	amorphous
130	Z	L-Val	Bz	-NH-	phenyl	bond	OH	a) b) sap.	NMR[h)]

Ex. No.	R_1	A	R_2	X	R_3	B	R_4	Process variant	m.p.
131	Z	L-Val	Bz	-NH-	cHex	bond	OH	a) b) sap.	220-225°
132	Z	L-Val	Bz	-NH-	Bu	bond	OH	a) b) sap.	202-205°
133	Z	L-Val	Bz	-NH-	2-phenylethyl	bond	OH	a) b) sap.	210-215°
134	Z	L-Val	Bz	-NH-	2-(indol-2-yl)-ethyl	bond	OH	a) b) sap.	194-199°
135	Z	L-Val	Bz	-NH-	1-naphthyl-methyl	bond	OH	a) b) sap.	186-192°
136	Z	L-Val	Bz	-NH-	4-MeO-Bz	bond	OH	a) b) sap.	197-202°
137	Z	L-Val	Bz	-NH-	4-Cl-Bz	bond	OH	a) b) sap.	198-204°
138	2-quinolyl-carbonyl	L-Val	Bz	-NH-	Bz	bond	OH	a) b) sap.	oil; NMR[h)]
139	Z	L-Val	Bz	-NH-	4-Br-Bz	bond	OH	a) b) sap.	202-207°
140	Z	L-Val	2-Ph-ethyl	-NH-	4-Cl-Bz	bond	OH	a) b) sap.	198-203°
141	Z	L-Val	Bz	-NH-	3-MeO-Bz	bond	OH	a) b) sap.	190-200°
142	Z	L-Val	Bz	-NMe-	3-phenylprop-2(E)-enyl	bond	OH	a) b) sap.	oil
143	BOC	bond	iBu	-NH-	phenyl	bond	OEt	a)	90-115°
144	Z	L-Val	Bz	-NH-	Bz	bond	OEt	b)	52-55°
145	BOC	L-Val	Bz	-S-	Bz	bond	OEt	b)	NMR[a)]
146	Z	L-Val	Bz	-NH-	Bz	L-Val	NHBz	a)	81-84°
147	Z	L-Val	Bz	-NH-	Bz	L-Leu	NHBz	a)	190-201°
148	Z	O-tBu-L-Ser	Bz	-NH-	Bz	L-Val	NHBz	a)	59-63°
149	Z	L-Val	iBu	-NH-	Bz	L-Phe	OMe	a)	NMR[b)]
150	Z	L-His	Bz	-NH-	Bz	L-Val	NHBz	a)	NMR[c)]
151	2-quinolyl-carbonyl	L-Asn	Bz	-NH-	Bz	L-Val	NHBz	a)	NMR[d)]

Ex. No.	R_1	A	R_2	X	R_3	B	R_4	Process variant	m.p.
152	Z	L-Ser	Bz	-NH-	Bz	L-Val	NHBz	a) b)	76-81°
153	Z	L-Val	Bz	-NH-	Bz	bond	OH	a) b)	187-193°
154	Z	L-tLeu	Bz	-NH-	Bz	bond	OH	a) b) sap.	124-130°
155	Z	L-tLeu	Bz	-NH-	Bz	bond	OEt	a) b)	54-58°
156	BOC	bond	Bz	-NH-	4-MeO-Bz	bond	benzimidazol-2-2-ylmethylamino	a) b)	105-109°
157	Z	L-tLeu	Bz	-NH-	Bz	bond	L-NHC(Ph)CH_2OH	a) b)	68-72°
158	BOC-NH$(CH_2)_5$CO-L-Val		Bz	-NH-	Bz	L-Val	NHBz	a) b)	dch 169-173°
159	BOC	bond	Bz	-NH-	4-Cl-Bz	bond	OH	a) sap.	213-216°

a) See Example 1a;
b) See Example 3a;
c) See Example 3b;
d) See Example 3c;
e) Two stereoisomers designated **a** and **b** are obtained;
f) Two diastereoisomers designated **a** and **b** are obtained;
g) A mixture of both stereoisomers is obtained;

h) NMR:
Example 25:
^{1}H-NMR: 0.75 (d,6H); 0.86 (2d,6H); 1.97 (sext,2H); 2.45-2.80 (m,4H); 3.10 (d,1H); 3.80-3.90 (m,2H); 4.00-4.15 (m,2H); 4.40 (dq,2H); 5.10 (AB,2H); 5.18 (d,2H); 6.85-7.40 (m,19H); 7.20 (d,1H); 7.36 (d,1H); 7.78 (d,1H); 8.50 (t,1H);

Example 29:
^{1}H-NMR: 0.70 (d,3H); 0.82 (d,3H); 0.87 (d,3H); 0.92 (d,3H); 1.80 (sext,1H); 2.01 (sext,1H); 2.97 (d,2H); 3.22 (d,1H); 3.55 (AB,2H); 3.72 (s,3H); 3.75-3.90 (m,2H); 4.15-4.23 (m,2H); 4.40 (dq,2H); 5.10 (bs,3H); 6.45 (bd,1H); 6.63 (bt,1H); 6.82 (d,1H); 7.08-7.40 (m,19H); 8.18 (d,1H);

Example 31:
^{1}H-NMR: 0.72 (d,3H); 0.78 (d,3H); 0.84 (d,3H); 0.90 (d,3H); 2.08 (m,2H); 2.85 (AB,2H); 3.24 (d,1H); 3.62 (dd,2H); 3.84 (m,2H); 4.40 (AB,2H); 4.61 (dd,1H); 5.08 (bs,3H); 6.28 (d,1H); 6.52 (t,1H); 6.64 (d,1H); 7.12-7.41 (m,20H);

Example 32 ($CDCl_3/CD_3OD$ 9:1):
^{1}H-NMR: 0.87 (d,3H); 0.93 (2d,6H); 0.97 (d,3H); 2.2-2.3 (m,2H); 2.83-2.96 (m,2H); 3.33 (d,1H); 3.88 (dd,1H); 4.25-4.33 (m,3H); 4.52 (s,2H); 6.94-6.99 (m,1H); 7.08-7.18 (5H); 7.2-7.36 (5H); 7.6-7.7 (m,2H); 7.8-7.85 (m,1H); 7.91 (dd,1H); 8.14 (dd,1H); 8.36 (d+m,2H); 8.60 (d,1H);
^{13}C-NMR: 17.55, 17.695, 19.27, 19.353, 29.98, 30.07, 37.18, 44.32, 51.89, 52.4, 58.813, 59.36, 63.506, 71.78, 118.59, 122.26, 122.36, 126.18, 127.21, 127.634, 128.146, 128.178, 128.283, 128.389, 129.013, 129. 368, 129.69, 130.226, 137.13, 137.61, 137.76, 138.75, 146.38, 148.59, 148.67, 156.88, 165.11, 171. 59, 171.66, 173.67;

Example 36:
^{1}H-NMR: 0.73, 0.86, 0.89 and 0.95 (4d, J=6Hz,12H); 2.07 and 2.23 (2oct, J=6Hz,2H); 2.96 (d,J=6.7Hz,2H); 3.25 (d,J=8Hz,1H); 3.59 (q,J=12Hz,2H); 3.84-3.93 (m,2H); 4.16-4.22 (m,2H); 4.35 and 4.45 (ABX, J_{AB}=15Hz,J_{AX}=J_{BX}=6Hz,2H); 4.92 (b,1H); 5.19 and 5.24 (AB,J=13Hz,2H); 5.21-5.26 (m,1H); 6.50-6.62 (m,2H); 7.15-7.35 (m,17H); 7.68 (t,J=6Hz,1H); 8.09 (d,J=9Hz,1H); 8.53 (d,J=5Hz,1H);

Example 37:
^{1}H-NMR: 0.86 (s,9H); 1.86 and 1.94 (2d,J=7Hz,6H); 2.00 (b,1H); 2.25 (oct,J=7Hz,1H); 2.97 (d,J=8Hz,2H); 3.29 (d,J=8Hz,1H); 3.52-3.63 (m,2H); 3.73 (d,J=8Hz,1H); 3.90 (d,J=6.4Hz,1H); 4.12 (q,J=7Hz,1H); 4.29 (dd,J=7 and 9Hz,1H); 4.33 and 4.51 (ABX,J_{AB}=15Hz,J_{AX}=5.4Hz,J_{BX}=6Hz,2H); 5.01 and 5.10 (AB,J=12Hz,2H); 5.08 (b,1H); 5.31 (d,J=8Hz,1H); 6.48 (d,J=7Hz,1H); 6.90-7.03 (m,1H); 7.08-7.39 (m,20H); 8.13 (d,J=9Hz,1H);

Example 38:
^{1}H-NMR: 0.91 and 0.97 (2d,J=7Hz,6H); 1.23 (t,J=6Hz,3H); 1.72 (b,1H); 2.32 (oct,J=7Hz,1H); 2.86 (m,2H); 3.30 (d,J=8.5Hz,1H); 3.56 and 3.71 (AB,J=13.6Hz,2H); 3.74 (dd,J=2 and 16Hz,1H); 4.12-4.22 (m,2H); 4.34-4.49 (m,2H); 6.58 (d,J=9Hz,1H); 6.96-7.18 (m,11H); 7.60-7.65 (m,1H); 7.78-7.96 (m,2H); 8.15-8.38 (m,3H); 8.63 (d,J=8.6Hz,1H);

Example 40:
^{1}H-NMR: a) diastereoisomer a: 0.69 (d,3H); 0.82 (d,3H); 0.88 (d,3H); 0.94 (d,3H); 1.70 (m,1H exchangeable); 2.03 (m,1H); 2.30 (m,1H); 2.90-3.00 (2dd,2H); 3.30 (d,1H,J=6.7Hz); 3.65 (dd,2H); 4.15 (m,1H); 4.25 (q,1H); 4.40 (dd,2H); 4.65 (p,1H exchangeable); 5.09 (s,2H); 5.13 (d,1H exchangeable); 6.59 (d,1H exchangeable); 7.10-7.40 (m,16H); 7.6 (ddd,1H); 8.08 (d,1H exchangeable); 8.43 (dd,1H,J=3.6Hz); 8.49 (d,1H,J=1.7Hz);
b) diastereoisomer b: 0.78 (d,3H); 0.79 (d,3H); 0.88 (d,3H); 0.94 (d,3H); 1.70 (m,1H exchangeable); 1.90 (m,1H); 2.25 (m,1H); 2.92 (m,2H); 3.10 (d,1H); 3.54 (AB,J_{AB}=12.5Hz,2H); 3.62 (d,1H); 3.80 (t,1H); 4.28 (dd,1H); 4.40 (d,2H); 4.60 (dd,1H); 5.15 (AB,J_{AB}=12.5Hz,2H); 5.45 (d,1H exchangeable); 6.50 (d,1H exchangeable); 7.05 (m,1H exchangeable); 7.10-7.40 (m,16H); 7.59 (ddd,1H); 8.45 (dd,1H); 8.50 (d,1H);

Example 42:
^{1}H-NMR: a) diastereoisomer a: 0.73 (d,3H); 0.87 (d,3H); 0.98 (s,9H); 1.70-2.00 (m,H exchangeable); 2.00-2.18 (m,1H); 2.85-3.00 (m,2H); 3.25 (d,J=8.5Hz,1H); 3.56 (s,2H); 3.88 (m,1H); 3.90-4.10 (m,1H); 4.10-4.50 (m,4H); 5.05 (s,2H); 5.22 (d,1H exchangeable); 6.44-6.54 (t,1H exchangeable); 6.80 (d,1H); 7.10-7.45 (m,20H); 8.34 (d,1H exchangeable);
b) diastereoisomer b: 0.72 (d,3H); 0.79 (d,3H); 1.05 (s,9H); 1.80-2.00 (m,1H); 2.80-3.00 (m,2H); 3.12 (d,J=9.4Hz,1H); 3.54 (s,2H); 3.66 (d,1H); 4.00-4.10 (dd,1H); 4.40-4.55 (m,4H); 4.70-4.95 (dd,2H); 5.21 (d,1H exchangeable); 7.00-7.40 (m,20H);
^{13}C-NMR: diastereoisomer b: 17.65, 19.42, 26.81, 31.05, 35.5, 38.36, 43.58, 51.32, 53, 60.92, 64.5, 66.97, 72.5, 77.2, 126.38-129.34 (C aromatic), 136.02, 137.86, 138.01, 138.73, 156.38, 169.91, 171.43, 174.14;

Example 43:
^{1}H-NMR: [0.8(d,diastereoisomer a); 0.90 (d, diastereoisomers a+b), 0.95 (d, diastereoisomer b), 6H]; [1.23 (s, diastereoisomer a), 1.38 (diastereoisomer b), 9H]; 2.10-2.20 (m,1H); 2.70-2.80 (m,2H); 3.20-4.60 (8H); 7.00-7.30 (m,11H); 7.55-7.70 (m,1H); 8.35-8.45 (m,2H);

Example 44:
^{1}H-NMR (DMSO): 0.88 (d,3H); 0.94 (d,3H); 1.33 (s,9H); 2.20-2.30 (m,1H); 2.80-2.90 (m,2H); 3.30 (d,1H); 3.60-3.80 (2d,2H); 3.80-3.90 (m,1H); 3.90-4.10 (m,1H); 4.40 (m,1H); 4.50 (m,2H); 7.00-7.40 (m,12H); 7.60 (ddd,1H); 8.45 (m,1H);

Example 45:
^{1}H-NMR: 0.85 (d,3H); 0.93 (d,3H); 1.28 (s,9H); 2.20-2.30 (m,1H); 2.80-3.00 (m,2H); 3.38 (d,1H); 3.50-4.60 (m,8H); 7.10-7.40 (m,12H); 8.50-8.60 (m,2H);

Example 46:
^{1}H-NMR: 0.96 (s,9H); 1.39 and 1.42 (2s,9H); 2.80-3.00 (m,2H); 3.12 and 3.24 (2d,1H); 3.50-4.10 (m,8H); 4.30-4.40 (m,2H); 7.10-7.50 (m,15H);

Example 51:
^{1}H-NMR: 0.73 (s,9H); 0.95 and 0.98 (2d,J=7Hz,6H); 1.65 (bs,1H); 2.30 (oct,J=7Hz,1H); 2.89 and 3.15 (ABX, J_{AB}=14Hz,J_{AX}=4Hz,J_{BX}=7.5Hz,2H); 2.94-3.08 (m,3H); 3.29 (d,J=7.5Hz,1H); 3.60 (d,J=7.5Hz,1H); 3.60 and 3.65 (AB,J_{AB}=12.5Hz,2H); 3.89 (dd,J=3.5Hz,J=7.5Hz,1H); 3.95-4.01 (m,1H); 4.22-4.33 (m,3H); 4.52-4.58 (m,1H); 5.13 (b,1H); 5.95 (bm,1H); 6.79 (t,J=6Hz,1H); 6.88 (d,J=7.5Hz,1H); 7.14-7.33 (m,20H); 8.01 (d,J=9Hz,1H);

Example 53:
^{1}H-NMR: 0.63, 0.89, 0.93, 0.95 (4d,J=7Hz,12H); 2.05 (dsp, J=3Hz,J=7Hz,1H); 2.19 (oct,J=7Hz,1H); 2.91-3.02 (m,2H); 3.20 (d,J=8Hz,1H); 3.55 and 3.58 (AB,J_{AB}=13Hz,2H); 3.88 (d,J=8Hz,1H); 3.91 (d,J=3Hz,1H); 4.18 (dd,J=6Hz,J=7Hz,1H); 4.35 (q,J=7.5Hz,1H); 4.42 (dd,J=2Hz,J=6Hz,2H); 6.45 (t,J=6Hz,1H); 7.03 (d,J=10Hz,1H); 7.18-7.35 (m,15H); 8.08 (d,J=8Hz,1H);

Example 56:
^{1}H-NMR: 0.78 (d,3H); 0.83 (d,3H); 0.97 (d,3H); 1.00 (d,3H); 1.98 (sext,1H); 2.35 (sext,1H); 2.95 (ABX,2H); 3.38 (d,1H); 3.65-3.76 (m,2H); 3.79 (s,3H); 3.84 (m,1H); 3.99 (m,1H); 4.17 (m,1H); 4.24 (dd,1H); 4.62 (ABX,2H); 5.11 (AB,2H); 5.19 (d,1H); 6.80-7.41 (m,20H); 7.96 (d,1H); 8.20 (bs,1H);

Example 59:
^{1}H-NMR ($CDCl_3$/CD_3OD 9:1): 0.76 (d,3H); 0.83 (d,3H); 0.97 (2d,6H); 1.94 (sext,1H); 2.20 (sext,1H); 2.78-2.92 (m,2H); 3.38 (d,1H); 3.58 (AB,2H); 3.79 (s,3H); 3.84 (d,1H); 3.90 (m,1H); 4.22 (d,1H); 4.25 (dd,1H); 4.61 (AB,2H); 5.10 (AB,2H); 6.82 (d,2H); 7.02-7.60 (m,16H);

Example 66 (DMSO):
^{1}H-NMR: 0.75 (d,6H); 0.87 (d,3H); 0.90 (d,3H); 1.80-2.00 (m,1H); 2.00-2.15 (m,1H); 2.50-2.70 (m,1H); 2.70-2.85 (m,1H); 3.00-3.20 (d,1H); 3.30-3.50 (m,2H); 3.50-3.60 (m,1H); 3.83 (t,1H); 4.20-4.40 (2m,2H); 4.40-4.65 (2dd,2H); 5.00-5.15 (AB,J_{AB}=12.4Hz,2H); 5.35 (d,1H exchangeable); 7.00-7.45 (m,19H); 7.52 (d,1H exchangeable); 7.60 (d,1H exchangeable); 7.90 (d,1H exchangeable);
^{13}C-NMR: 17.85, 18.25, 19.3, 29.92, 30.38, 37.04, 51.3, 51.8, 58, 60.75, 63.79, 65.5, 71.06, 74.1, 11??.2, 118.35, 121.1, 121.8, 124.8-129.16 (C aromatic); 136.9, 138.9, 140.1, 151.8, 156.2, 170.78, 171.3, 173.2;

Example 67 (DMSO):
^{1}H-NMR: 0.74 (d,6H); 0.87 (d,3H); 0.89 (d,3H); 1.80-2.20 (m,2H); 2.40-2.70 (m,1H); 2.70-2.95 (m,1H); 3.10 (d,1H); 3.30-3.50 (m,2H); 3.50-3.60 (m,1H); 3.75-3.85 (t,1H); 4.20-4.40 (m,2H); 4.40-4.65 (m,2H);

4.90-5.10 (AB, J_{AB}=12.5Hz,2H); 5.36 (d,1H exchangeable); 7.05-7.25 (m,9H); 7.25-7.6 (m,9H+1H exchangeable); 7.86 (d,1H exchangeable); 8.65 (t,1H exchangeable); 12.17 (s,1H exchangeable);

^{13}C-NMR: 17.84, 18.29, 19.26, 19.3, 29.86, 30.33, 37.04, 50.37, 51.73, 58.05, 60.75, 63.6, 65.5, 70.96, 111.19, 118.35, 119.68, 121.07, 121.86, 125.825, 127.7, 127.765, 127.99, 128.31, 129.15, 130.31, 130.87, 134.11, 136.93, 138.9, 139.56, 143, 151.8, 156.2, 162.3, 170.7, 171.3, 173.2;

Example 73:

^{1}H-NMR: 1.80 (bs,1H); 2.99 (d,J=8Hz,2H); 3.16 (d,J=9Hz,1H); 3.41 and 3.50 (AB,J=13Hz,2H); 3.78 (d,J=10Hz,1H); 4.12 (q,J=8Hz,1H); 4.33 and 4.40 (ABX,J_{AB}=14Hz,J_{AX}=J_{BX}=6Hz,2H); 5.00-5.28 (m,3H); 5.40 (d,J=10Hz,1H); 6.98-7.42 (m,20H); 7.84 (t,J=5.5Hz,1H);

Example 74:

^{1}H-NMR: 0.92 (d,6H); 1.20-1.38 (m,2H); 1.40 (s,9H); 1.53-1.72 (m,1H); 3.01-3.22 (m,2H); 3.10 (d,1H); 3.45 and 3.60 (AB,2H); 3.75 (d,1H); 3.78 (s,3H); 3.80-3.95 (m,1H); 4.80-4.95 (m,1H); 7.02-7.38 (m,10H);

Example 76:

^{1}H-NMR: 0.92 (d,6H); 1.30 (t,3H); 1.30-1.41 (m,2H); 1.65 (sept,1H); 3.35 (dd,1H); 3.65 and 3.85 (AB,2H); 3.67-3.73 (m,1H); 3.80-3.92 (m,1H); 4.22 (q,2H); 4.65 (d,1H); 7.20-7.35 (m,5H);

Example 77:

^{1}H-NMR: 1.28 (t,3H); 1.38 (s,9H); 1.72 (bs,1H); 2.80-3.03 (m,2H); 3.33 (d,1H); 3.60 and 3.80 (AB,2H); 3.72 (d,1H); 4.04 (q,1H); 4.18 (q,2H); 4.80 (d,1H); 7.15-7.40 (m,10H);

Example 78:

^{1}H-NMR: 0.82 (2d,6H); 1.08 (t,3H); 2.10 (sext,1H); 2.95 (m,2H); 3.90 (m,2H); 4.05 (d,1H); 4.10 (q,2H); 4.28 (dt,1H); 5.12 (s,2H); 6.65 (d,2H); 6.78 (t,1H); 7.08-7.42 (m,15H);

Example 81:

^{1}H-NMR: 0.64 (d,3H); 0.82 (t,3H); 1.85 (sext,1H); 2.61-2.83 (m,2H); 3.24 (d,H); 3.62-3.80 (m,2H); 3.94 (d,1H); 4.21 (q,2H); 4.25-4.41 (m,2H); 5.07 (d,1H); 5.10 (s,2H); 5.97 (d,1H); 7.00-7.61 (m,14H); 7.78 (m,1H); 7.81 (d,1H); 8.24 (d,1H);

Example 82:

^{1}H-NMR: 0.78 (d,3H); 0.84 (d,3H); 1.21 (t,3H); 1.95 (sext,1H); 2.60-3.08 (m,6H); 3.10 (d,1H); 3.62 (dd,1H); 3.75 (dd,1H); 4.17 (q,2H); 4.23 (dq,1H); 5.12 (s,2H); 5.17 (m,1H); 6.17 (d,1H); 6.95-7.40 (m,14H); 7.58 (d,1H); 8.39 (bs,1H);

Example 83:

^{1}H-NMR: 0.75 (d,3H); 0.87 (d,3H); 1.26 (t,3H); 2.17 (sext,1H); 2.84 (AB,2H); 3.22 (d,1H); 3.43-3.81 (m,3H); 3.90 (dd,1H); 4.18 (q,2H); 4.45 (dd,1H); 5.10 (s,2H); 5.20 (d,1H); 6.41 (d,1H); 7.08-7.40 (m,11H); 7.69 (d,1H); 8.50 (m,2H);

Example 84:
^{1}H-NMR: 0.78 (d,3H); 0.85 (d,3H); 1.22 (t,3H); 2.00 (sext,1H); 2.75-3.00 (m,5H); 3.12 (dd,1H); 3.28 (d,1H); 3.65 (dd,1H); 3.91 (dq,1H); 4.08 (dd,1H); 4.18 (q,2H); 5.10 (s,2H); 5.38 (d,1H); 7.10-7.39 (m,12H); 7.64 (dt,1H); 8.15 (d,1H); 8.22 (m,1H);

Example 91:
^{1}H-NMR: 0.80 (d,3H); 0.92 (d,3H); 1.34 (t,3H); 2.15 (m,4H); 2.82-3.22 (m,5H); 3.84 (m,2H); 4.23 (dq,2H); 4.70 (dd,1H); 5.10 (s,2H); 5.20 (d,1H); 6.01 (dt,1H); 6.40 (d,1H); 7.00-7.40 (m,16H);

Example 93:
^{1}H-NMR: 1.27 (t,3H); 1.42 (s,9H); 2.67-3.15 (AB,2H); 3.24 (d,1H); 3.47 (d,1H); 3.70 (AB,2H); 3.84 (dd,1H); 4.17 (q,2H); 4.22 (q,1H); 4.78 (q,1H); 7.15-7.40 (m,10H);

Example 97:
^{1}H-NMR: 0.72 (d,3H); 0.80 (s,9H); 0.87 (d,3H); 2.18 (sext,1H); 2.88-3.16 (m,5H); 3.62 (AB,2H); 3.76 (d,1H); 3.81 (s,3H); 4.00 (dd,1H); 4.45 (bq,1H); 5.11 (s,2H); 5.08-5.18 (m,1H); 6.58 (d,1H); 6.83 (d,2H); 7.15-7.40 (m,12H); 7.80 (bt,1H);

Example 98:
^{1}H-NMR: 1.27 (s,9H); 2.80-3.12 (m,2H); 3.38 (d,1H); 3.63 (d,1H); 3.69 (s,3H); 3.81-3.94 (m,1H); 4.46 (bq,1H); 4.90 (d,1H); 7.03-7.40 (m,10H);

Example 106:
^{1}H-NMR: 0.83 (s,9H); 0.95 and 1.01 (2d,J=7Hz,6H); 1.59 (bs,1H); 2.32 (oct,J=7Hz,1H); 2.96-3.06 (m,2H); 3.31 (d,J=7.5Hz,1H); 3.61 and 3.65 (AB,J=14Hz,2H); 3.77 (d,J=7.5Hz,1H); 3.92 (d,J=7.5Hz,1H); 4.06-4.12 (m,1H); 4.28 (dd,J=6Hz and 9Hz,1H); 4.35 and 4.58 (ABX,J_{AB}=15Hz,J_{AX}=6.5Hz,J_{BX}=5Hz,2H); 4.40 and 4.47 (AB,J=15Hz,2H); 4.98 (bs,1H); 5.98 (d,J=7.5Hz,1H); 6.73 (t,J=6Hz,1H); 6.90-6.97 (m,3H); 7.02-7.07 (m,1H); 7.13-7.37 (m,17H); 8.09 (d,J=9Hz,1H);

Example 108:
^{1}H-NMR: 0.84 (s,9H); 0.85 (s,3H); 0.88 and 0.92 (2d,6H); 1.20-1.41 (m,25H); 1.48-1.62 (m,1H); 1.92 (bs,1H); 2.01-2.21 (m,2H); 2.28 (oct,1H); 3.00 (d,J=8.5Hz,2H); 3.26 (d,J=8Hz,1H); 3.58-3.65 (m,2H); 3.83-3.98 (m,2H); 4.02-4.18 (m,1H); 4.23-4.39 (m,2H); 4.48-4.60 (m,1H); 5.03 (bs,1H); 5.90 (d,J=7Hz,1H); 6.32 (d,J=7.5Hz,1H); 7.03 (t,1H); 7.10-7.37 (m,15H); 8.08 (d,J=9Hz,1H);

Example 114:
^{1}H-NMR: 0.83 (s,9H); 0.92 and 0.97 (2d,J=7Hz,6H); 2.24 (oct,J=7Hz,1H); 2.95 and 3.01 (ABX,J_{AB}=14Hz,J_{AX}=7Hz,J_{BX}=8Hz,2H); 3.23 (d,J=8Hz,1H); 3.56 and 3.63 (AB,J_{AB}=13Hz,2H); 3.92 (d,J=8Hz,1H); 4.23 (dd,J=3Hz and 9Hz,1H); 4.29 (q,J=8.5Hz,1H); 4.42 and 4.45 (ABX,J_{AB}=14Hz,J_{AX}=J_{BX}=6Hz,2H); 5.10 (bs,1H); 6.72 (bm,1H); 7.18-7.36 (m,15H); 8.05 (d,J=9Hz,1H);

Example 116:
^{1}H-NMR: 0.58 and 0.87 (2d,J=7Hz,6H); 1.28 (t,J=7Hz,3H); 1.50 (b,3H); 2.09-2.24 (m,1H); 2.97 (d,J=8Hz,2H); 3.08 (d,J=4Hz,1H); 3.22 (d,J=8Hz,1H); 3.54-3.83 (m,4H); 4.23 (dq,J=3 and 8Hz,2H); 7.08-7.38 (m,10H); 7.51 (d,J=8Hz,1H);

Example 118:
^{1}H-NMR: 0.88 (d,6H); 1.38 (t,2H); 1.70 (sept,1H); 3.00-3.20 (m,2H); 3.20 (d,1H); 3.22-3.35 (m,1H); 3.58 (AB,2H); 3.67 (dd,1H); 3.71 (s,3H); 4.82 (dd,1H); 7.15-7.35 (m,10H); 7.90 (d,1H);

Example 120:
^{1}H-NMR ($CDCl_3/CD_3OD$ 9:1): 0.97 (d,3H); 1.04 (d,3H); 2.26 (sext,1H); 2.48-2.81 (AB,2H); 3.21 (m,1H); 3.43 (d,1H); 3.69 (d,2H); 3.74 (dd,1H); 4.30 (d,1H); 4.42 (AB,2H); 7.08-7.38 (m,12H)

Example 130:
^{1}H-NMR (DMSO): 0.68 (d,3H); 0.76 (d,3H); 1.87 (sext,1H); 2.70,2.80 (2dd,2H); 4.34 (q,1H); 5.07 (s,2H); 7.08-7.60 (m,15H); 7.70 (d,1H);

Example 138 (DMSO):
^{1}H-NMR: 0.79 and 0.81 (2d,J=8Hz,6H); 2.02-2.18 (m,1H); 2.64-2.86 (m,2H); 3.80-4.16 (m,3H); 4.24-4.58 (m,2H); 6.90-7.03 (m,1H); 7.04-7.30 (m,4H); 7.30-7.54 (m,5H); 7.70-7.82 (m,1H); 7.82-7.98 (m,1H); 8.12-8.39 (m,4H); 8.58-8.70 (m,1H);
^{13}C-NMR: 18.27, 19.24, 30.06, 37.46, 50.34, 51.28, 61.12, 62.32, 65.68, 70.98, 74.2, 120.6, 126, 127.9, 128.2, 128.4, 129.3, 130.9, 131.16, 136.9, 137.24, 138.8, 156.23, 171.56, 173.3;

The compounds used as starting materials can be prepared e.g. as follows:

A: **4(S)-[(N-Benzyloxycarbonyl-L-valinoyl)amino]-2,3-epoxy-5-phenyl-pentanoic acid ethyl ester**

[Formula II: R_1 = Z; A = L-Val; R_2 = Bz; B = a bond; R_4 = OEt; configuration at 4 position: S]

a) Acylation:

3.2 g of **L-phenylalaninol** (an intermediate of formula III) are added to a solution of 7.44 g of **N-benzyloxycarbonyl-L-valin-p-nitrophenylester** (an intermediate of formula R_1A-Q wherein Q is p-nitrophenyloxy) in 50 ml of dimethylformamide. 2 g of triethylamine are added and the reaction mixture is stirred at room temperature for 3 days. After evaporation of the solvent the residue is dissolved in dichloromethane and carefully washed repeatedly with 0.1 N NaOH, then once with water and dried. The solution is filtered, the solvent evaporated and the residue chromatographed on silicagel (solvent: dichloromethane/methanol 95:5). **N-Benzyloxycarbonyl-L-valinoyl-L-phenylalaninol** (an intermediate of formula IV) (m.p. 154-156°) is obtained.

b) Oxidation and Wittig reaction:

3.12 ml of **oxalylchloride** are dissolved in 40 ml of dry dichloromethane and cooled to -55°. 2.81 ml of dimethylsulfoxide are carefully added dropwise and then 6.98 g of **product of step a)** dissolved in 40 ml of dichloromethane and 3.125 ml of **dimethylsulfoxide** are added at -50°. The reaction mixture is stirred at -60° for one hour, reacted with **triethylamine** and stirred until it reaches room temperature. After dilution with 200 ml of dichloromethane the mixture is washed with aqueous 1N HCl solution, dried and the solvent evaporated. The residue is dissolved in toluene, 6.32 g of **ethoxycarbonylmethylenetriphenylphosphorane** are added and the reaction mixture is heated to 80° for 1 hour. After evaporation of the solvent the residue is chromatographed on silicagel

(solvent: toluene/ethyl acetate 4:1). **4(S)-[(N-Benzyloxycarbonyl-L-valinoyl)amino]-5-phenylpent-2(E)-enoic acid ethyl ester** (an intermediate of formula VI) (m.p. 161-165°) is obtained.

c) Epoxidation:

3 g of **product of step b)** are dissolved in 30 ml of dichloromethane. 1.373 g of **m-chloroperbenzoic acid** are added and the reaction mixture is stirred for 5 days. After evaporation of the solvent the residue is chromatographed on silicagel (solvent: toluene/ethyl acetate 4:1). The **title compound** (**compound A**) (an intermediate of formula IIa) is obtained (m.p. 164-167°).

The following intermediates of formula II are obtained in analogous manner (the configuration in 4 position is S):

Compound	R_1	A	R_2	B	R_4	m.p.
B	BOC	bond	iBu	bond	OEt	NMR[a)]
C	BOC	bond	Bz	bond	OEt	55-61°
D	Z	L-Val	2-phenylethyl	bond	OEt	NMR[b)]
E	Z	L-Val	Bz	L-Val	NHBz	166-175°
F	Z	L-Val	Bz	bond	OH	NMR[c)]

a) ^{1}H-NMR: 0.97 (2d,6H); 1.29 (t,3H); 1.44 (s,9H); 1.40-1.53 (m,2H); 1.63-1.80 (m,1H); 3.25 (bs,1H); 3.35 (bs,1H); 4.10 (bq,1H); 4.22 (dq,2H);

b) ^{1}H-NMR: 0.87 (d,3H); 0.98 (d,3H); 1.28 (t,3H); 1.82-2.06 (m,2H); 2.20 (sext,1H); 2.60-2.78 (m,2H); 3.21-3.37 (m,2H); 3.95 (dd,1H); 4.21 (q,2H); 4.38-4.50 (m,1H); 5.07-5.20 (m,3H); 5.92 (d,1H); 7.10-7.42 (m,10H);

c) ^{1}H-NMR: 0.70 (d,3H); 0.76 (d,3H); 1.70-1.90 (m,1H); 2.60-2.90 (m,2H); 3.00-3.15 (m,1H); 3.18-3.20 (m,1H); 3.60-4.30 (m,2H); 5.10 (s,2H); 7.00-7.50 (m,11H); 7.86 (d,1H).

G: D,L-tert-Leucine benzylamide

[Formula H - BR_4: B = D,L-tLeu; R_4 = NHBz]

a) To a solution of 1 g of **N-(tert-butoxycarbonyl)-D,L-tert-leucine** in 60 ml of dichloromethane are added at room temperature 980 mg of dicyclohexylcarbodiimide, 550 mg of N-hydroxysuccinimide, 0.53 ml of N-methylmorpholine and 0.57 ml of **benzylamine**. After 24 hours stirring at room temperature the solution is filtered, the solvent evaporated and the residue chromatographed on silicagel (solvent: toluene/ethyl acetate 5:1). **N-(tert-Butoxycarbonyl)-D,L-tert-leucine benzylamide** is obtained (solid):

^{1}H-NMR: 0.98 (s,9H); 1.4 (s,9H); 3.89 (d,1H); 4.3-4.6 (2dd,2H); 5.35 (d,1H); 6.55 (m,1H); 7.2-7.4 (m,5H).

b) 1.7 g of **product of step a)** are dissolved in 50 ml of dichloromethane , 10 ml of **trifluoroacetic acid** are added, the mixture is stirred for 4 hours and the solvent is removed. The residue is dissolved in ethyl acetate and washed with a saturated solution of sodium bicarbonate, then brine. The organic layer is dried, the solvent removed and the **title compound** (**compound G**) is obtained (oil):

^{1}H-NMR: 0.98 (s,9H); 3.05 (s,1H); 4.4 (s,2H); 7.2-7.4 (m,5H);
^{13}C-NMR ($CDCl_3$ + drops CD_3OD): 26.35, 34.05, 63.87, 127.3, 127.74, 128.5, 138.04, 173.7.

The following intermediates of formula H - BR_4, which may suitably be in protected form, are obtained in analogous manner:

Compound	B	R_4	m.p.
H	L-Val	3-pyridyl-methylamino	oil; NMR[a)]
I	L-Val	2-pyridyl-methylamino	oil; NMR[b)]
J	L-Val	4-pyridyl-methylamino	oil; NMR[c)]
K	L-Val	4-Br-benzylamino	71-75°
L	-NBC(-CH_2CH_2-)CO-	NHBz	oil; NMR[d)]

Compound	B	R_4	m.p.
M	L-Val	benzimidazol-2-ylmethylamino	oil; NMR[e]
N	L-Val	2-(4-OH-phenyl)-ethylamino	oil; NMR[f]
O	L-Val	2-(4-morpholinyl)-ethylamino	oil; NMR[g]
P	L-Val	benzimidazol-2-ylmethoxy	oil; NMR[h]
Q	L-Val	5-NO_2-benzimidazol-2-ylmethoxy	oil; NMR[i]
R	L-Val	5,6-diCl-benzimidazol-2-ylmethoxy	oil; NMR[j]
S	L-Val	2-(indol-3-yl)-ethylamino	81-86°

a) ^{1}H-NMR: 0.82 (d,J=7Hz,3H); 1.00 (d,J=7Hz,3H); 2.30-2.50 (m,1H); 3.31 (d,J=3.6Hz,1H); 4.40-4.60 (ddd,2H); 7.25-7.35 (m,2H); 7.60-7.70 (ddd,1H); 7.80-7.90 (m,1H); 8.53 (dd,J=4.8 and 1.6Hz,1H); 8.55 (d,J=2.25Hz,1H);

b) ^{1}H-NMR: 0.88 (d,J=7Hz,3H); 0.99 (d,J=7Hz,3H); 2.00-2.20 (m,1H); 3.30 (d,J=4.8Hz,1H); 4.54 (s,2H); 7.10-7.40 (m,2H); 7.60-7.70 (ddd,1H); 8.20-8.30 (m,1H); 8.30 (d,1H);

c) ^{1}H-NMR: 0.88 (d,J=7Hz,3H); 0.95 (d,J=7Hz,3H); 2.10-2.30 (m,1H); 3.23 (d,J=4.6Hz,1H); 4.46 (s,2H); 7.25 (d,2H); 8.45 (d,2H);

d) ^{1}H-NMR: 0.75-0.90 (m,2H); 1.45-1.55 (m,2H); 4.40-4.50 (d,2H); 7.20-7.40 (m,5H); 7.90-8.10 (bs,1H);

e) ^{1}H-NMR (DMSO): 0.80 (d,3H); 0.89 (d,3H); 1.85-2.10 (m,1H); 3.06 (d,1H); 4.51 (s,2H); 7.10-7.20 (m,2H); 7.45-7.55 (m,2H); 8.50 (bs,1H);

f) ^{1}H-NMR (DMSO): 0.74 (d,3H); 0.81 (d,3H); 1.82 (sext,1H); 2.58 (t,2H); 2.88 (d,1H); 3.14-3.30 (m,2H); 6.67 (d,2H); 7.00 (d,2H); 7.82 (bt,1H);

g) ^{1}H-NMR ($CDCl_3/D_2O$): 0.78 (d,3H); 1.84 (sext,1H); 2.31-2.42 (m,6H); 2.95 (d,1H); 3.18-3.31 (m,2H); 3.54-3.62 (m,4H);

h) ^{1}H-NMR: 0.84 (d,3H); 0.89 (d,3H); 1.80-2.00 (sext,1H); 3.00-3.50 (d,J=4.6Hz,1H); 5.30 (s,2H); 7.00-7.20 (m,2H); 7.40-7.60 (m,2H);

i) ^{1}H-NMR: 0.84 (d,3H); 0.89 (d,3H); 1.80-2.00 (m,1H); 3.26 (d,J=5.4Hz,1H); 5.37 (s,2H); 7.74 and 7.67 (2d,J=9Hz,1H); 8.00-8.20 (2dd,1H); 8.40 and 8.47 (2d,1H);

j) ^{1}H-NMR: 0.83 (d,3H); 0.89 (d,3H); 1.80-2.00 (m,1H); 3.24 (d,J=5.4Hz,1H); 5.36 (s,2H); 7.74 (s,2H);

T: N-Benzyloxycarbonyl-L-tert-leucine-N-hydroxysuccinimide ester

[Formula R_1A - Q: R_1 = Z; A = L-tLeu;
Q = N-hydroxysuccinimid-2-yloxy]

2.6 g of **N-hydroxysuccinimide** and 4.6 g of dicyclohexylcarbodiimide are added to a solution of 6 g of **N-benzyloxycarbonyl-L-tert-leucine** in 70 ml of dioxane. The mixture is stirred for 12 hours at room temperature, the solvent is evaporated, the residue is suspended in ethyl acetate, the urea is removed by filtration and the solvent is evaporated. The **title compound** (compound T) is obtained:

^{1}H-NMR: 1.10 (s,9H); 2.84 (s,4H); 4.52 (d,J=10Hz,1H); 5.03-5.12 (m,2H); 5.34 (d,J=10Hz,1H); 7.26-7.40 (m,5H).

The following intermediate of formula R_1A - Q is obtained in analogous manner:

Compound	R_1	A	Q	m.p.
U	2-pyridyl-methoxycarbonyl	L-Val	Su	white solid; NMR[a)]

a) ^{1}H-NMR: 1.09 and 1.11 (2d, J=7Hz, 6H); 2.38 (oct, J=7Hz, 1H); 2.82 and 2.84 (2s,4H); 4.62 (dd, J=5Hz, J=7.5Hz, 1H); 5.28 (s,2H); 7.25-7.42 (m,3H); 7.72-7.81 (m,1H).

The compounds of formula I in free form and, where salt forms exist, in pharmaceutically acceptable salt, e.g. acid addition salt form, possess interesting pharmacological properties. They are therefore indicated for use as pharmaceuticals. In particular, they exhibit antiviral activity, especially HIV-1 protease inhibiting activity, whereby they show only low or inexistent inhibiting effect against human proteases such as renin or pepsin.

This activity can be shown in the following tests:

1. HIV-proteinase inhibition

Inhibition of peptide cleavage by HIV-proteinase is measured as described in A.Richards et al., J.Biol.Chem. 265 (1990) 7733-7736 and L.H.Philip et al., Biochem.Biophys.Res.Commun. 171 (1990) 439-444. Briefly, the peptide H-Lys-Ala-Arg-Val-Leu-Nph-Glu-Ala-Nle-NH_2 (where Nph is p-nitrophenylalanine and Nle is norleucine) is used as substrate for recombinant HIV-1 or HIV-2 proteinase. Cleavage occurs between the Leu and Nph residues. The reaction is followed spectrophotometrically by the decrease in extinction at 300 nm which is observed upon cleavage.

In this test the compounds exhibit K_i values of from about 3 nM to about 1 µM for HIV-1, and of from about 30 nM to about 10 µM for HIV-2.

2. Inhibition of cellular HIV-induced cytopathic effect

Inhibition of the HIV-1 (HTLV III_B)-induced cytopathic effect is measured in MT4 cells as described in R.Pauwels et al., J.Virol.Methods 20 (1988) 309-321. Briefly, an HTLV-1 transformed T4 cell line, MT4, which has been shown previously to be highly susceptible to HIV infection, serves as the target cell line. Inhibition of HIV-induced cytopathic effect is used as the end point. The viability of both HIV- and mock-infected cells is assessed spectrophotometrically via the in situ reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). The comparison of the effects of various concentrations of the compound on HIV- versus mock-infected cells allows the determination of minimum toxic (MTC) and minimum virus-inhibitory (MIC) concentrations.

In this test the compounds exhibit IC_{50} values of from about 5 nM to about 350 nM. Thus the compounds of Examples 56 and 59 exhibit IC_{50} values of, respectively, 49 nM and 12 nM against HIV-1 strains, and the compound of Example 37 is effective with an IC_{50} value of 150 nM.

The compounds of the invention in free form and, where salt forms exist, in pharmaceutically acceptable salt form are therefore indicated for use as pharmaceuticals, particularly as agents against HIV-proteinase, e.g. in the prophylaxy and treatment of retroviral infections. For this use the effective dosage will, of course, vary depending on the particular compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds are administered at a daily dosage of from about 0.02 mg/kg to about 50 mg/kg animal body weight, suitably given in divided dosages two to four times daily. For most larger mammals the total daily dosage is from about 1 mg to about 3500 mg, e.g. from about 1 mg to about 500 mg or about 10 mg to about 100 mg. The compounds may be administered in similar manner to known standards for use in such indications.

The compounds are also indicated for use in treating non-human animals infected with a retrovirus, such as cats infected with feline leukemia virus, feline infectious peritonitis virus, calicivirus, rabies virus, feline immunodeficiency virus, feline parvovirus (panleukopenia virus), and feline chlamydia. Exact dosages, forms and modes of administration of the compounds to non-human animals would be apparent to one of ordinary skill in the art, e.g. a veterinarian.

The compounds of Examples 29, 36, 37, 51, 56, 59, 66, 67 and 106, especially of Examples 56 and 59, i.e. N-{[4(S)-[(N-benzyloxycarbonyl-L-valinoyl)amino]-3-hydroxy-2-(3-methoxybenzylamino)-5-phenyl]pentanoyl}-L-valine-N-(methyl-2-benzimidazolyl)amide and, respectively, the corresponding 4-methoxy position isomer are the preferred compounds as anti HIV-proteinase agents. It is indicated that for this indication these compounds may be administered to larger mammals, for example humans, by

similar modes of administration at similar or lower dosages than employed with standards for such indications.

The invention therefore also concerns a method of treating retroviral diseases, especially diseases caused by HIV which comprises administering to a subject in need of such treatment a prophylactically or therapeutically effective amount of a compound of formula I in free form or, where salt forms exist, in pharmaceutically acceptable salt, e.g. acid addition salt form, as well as a compound of formula I in free form or, where salt forms exist, in pharmaceutically acceptable salt form for use as a pharmaceutical, especially as an agent against HIV-proteinase.

The compounds may be admixed with conventional pharmaceutically acceptable diluents and carriers and, optionally, other excipients and administered e.g. orally in such forms as tablets or capsules. The compounds may alternatively be administered parenterally or intravenously. The concentrations of active substance will, of course, vary depending i.a. on the compound employed, the treatment desired and the nature of the form.

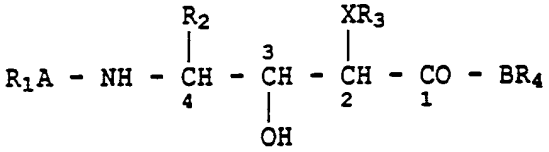
The invention thus also includes a pharmaceutical composition comprising a compound of formula I in free form or, where salt forms exist, in pharmaceutically acceptable salt, e.g. acid addition salt form, together with at least one pharmaceutically acceptable carrier or diluent.

It further concerns a process for the preparation of a medicament against retroviral diseases which comprises mixing a compound of formula I in free form or, where salt forms exist, in pharmaceutically acceptable salt, e.g. acid addition salt form, together with a pharmaceutically acceptable carrier or diluent, and the use of such a compound in the manufacture of a medicament against retroviral diseases.

It further concerns a compound of formula I in free form or, where salt forms exist, in pharmceutically acceptable salt, e.g. acid addition salt form, for use as a pharmaceutical, particularly for use in the treatment of retroviral diseases.

C L A I M S :

1. A compound of formula I



I

wherein

A and B independently are a bond or an optionally substituted aminoacyl moiety;

R_1 is hydrogen; an amino protecting group; or a group of formula R_6Y- wherein

R_6 is hydrogen or an optionally substituted alkyl, alkenyl, alkinyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl group; and

Y is -CO-; -NHCO-; -NHCS-; $-SO_2-$; -O-CO-; or -O-CS-;

R_2 is the side chain of a natural amino acid; an alkyl, arylalkyl, heteroarylalkyl or cycloalkylalkyl group; or trimethylsilylmethyl, 2-thienylmethyl or styrylmethyl;

R_3 is an optionally substituted alkyl, alkenyl, alkinyl, cycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl group;

R_4 is a group of formula $-OR_7$ or $-NHR_7$ wherein

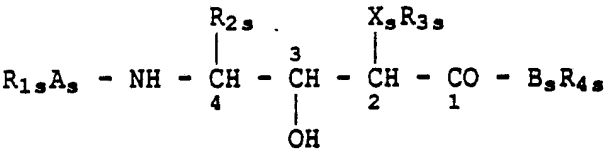
R_7 has the significance indicated above for R_6; and

X is -S- or $-NR_5-$ wherein

R_5 is hydrogen, methyl, formyl or acetyl;

in free form or, where such forms exist, in salt form.

2. A compound according to claim 1 of formula Is



Is

wherein

R_{1s} is hydrogen; phenylalkyloxycarbonyl of altogether 8 to 10 carbon atoms; alkyloxycarbonyl of altogether 2 to 10 carbon atoms; quinolylcarbonyl or quinolylsulfonyl; pyridylmethoxycarbonyl; aminocaproyl optionally protected by tert-butoxycarbonyl; 9-fluorenylmethoxycarbonyl (FMOC); phenyllactoyl; isovalerianoyl; phenoxymethylcarbonyl; palmitoyl; or 4-hydroxyphenylpropionyl;

A_s is a bond; a natural α-aminoacyl moiety; the corresponding D optical isomer form; L- or D-tert-leucine; O-tert-butyl-L-serine; or L-2-aminobutanoyl;

R_{2s} is alkyl of 3 or 4 carbon atoms or phenylalkyl of altogether 7 to 9 carbon atoms;

X_s is -S- or -NR_{5s}- wherein R_{5s} is hydrogen or methyl;

R_{3s} is alkyl of 3 to 5 carbon atoms; cycloalkyl of 5 to 7 carbon atoms optionally monosubstituted by hydroxy; phenyl; phenylalkyl of altogether 7 to 9 carbon atoms optionally monosubstituted in the phenyl ring by hydroxy, alkoxy of 1 to 3 carbon atoms, halogen of atomic number of from 9 to 35, or phenyl; a pyridylalkyl, indolylalkyl or naphthylalkyl group of 1 to 3 carbon atoms in the alkylene part; or phenylalkenyl of 2 to 4 carbon atoms in the alkenylene part;

B_s is a bond; a natural α-aminoacyl moiety; the corresponding D optical isomer form; L- or D-tert-leucine; or aminocyclopropan-1-carbonyl;

R_{4s} is hydroxy; an alkoxy or alkylamino group of 1 to 5 carbon atoms; phenylalkylamino of altogether 7 to 9 carbon atoms optionally monosubstituted in the phenyl ring or in the alkylene part by hydroxy, or monosubstituted in the phenyl ring by halogen of atomic number of from 9 to 35; benzimidazolylalkoxy or benzimidazolylalkylamino of 1 to

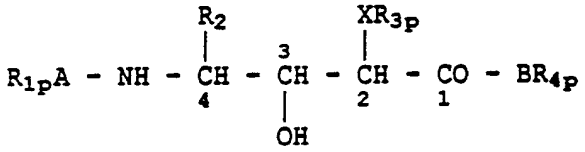
3 carbon atoms in the alkylene part optionally mono- or disubstituted in the aryl part by halogen of atomic number of from 9 to 35 or nitro; or an indolylalkylamino, pyridylalkylamino or morpholinylalkylamino moiety of 1 to 3 carbon atoms in the alkylene part; and

the configuration in 4 position is S,

in free form or, where such forms exist, in salt form.

3. A compound according to claim 1 of formula I wherein R_1 is benzylyoxycarbonyl, 2-pyridylmethoxycarbonyl, phenyllactoyl or phenoxymethylcarbonyl, A is L-valine or L-tert-leucine, R_2 is benzyl, X is -NH-, R_3 is benzyl, 3- or 4-methoxybenzyl or 4-bromobenzyl, B is L-valine and R_4 is benzylamino or benzimidazol-2-ylmethylamino, and the carbon atom in 4 position has the S configuration, in free form or, where such forms exist, in salt form.

4. A compound according to claim 1 of formula Ip_1



Ip_1

wherein

A, B, R_2 and X are as defined in claim 1;

R_{1p} with the exception of hydrogen has the significance indicated in claim 1 for R_1;

R_{3p} with the exception of optionally substituted cycloalkyl has the significance indicated in claim 1 for R_3; and

R_{4p} is hydroxy or a group of formula $-OR_7$ or $-NHR_7$ as defined in claim 1;

in free form or, where such forms exist, in salt form.

5. A compound according to claim 1 of formula I as defined in claim 1 with the exception that R_4 is hydroxy or a group of formula $-OR_7$ or $-NHR_7$ as defined in claim 1, in free form or, where such forms exist, in salt form.

6. The compound according to claim 1 of formula I wherein the configuration at the carbon atom in 4 position is S, R_1 is benzyloxycarbonyl, A is L-valine, R_2 is benzyl, X is -NH-, B is L-valine, R_4 is benzimidazol-2-ylmethylamino and R_3 is 3-methoxybenzyl, or the correspondig 4-methoxy position isomer, in free form or, where such forms exist, in salt form.

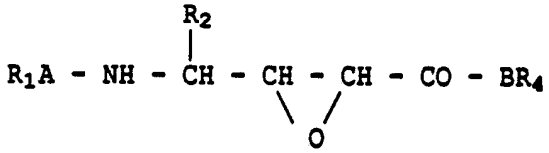
7. The compound according to claim 1 of formula I wherein the configuration at the carbon atom in 4 position is S, R_2 is benzyl, X is -NH-, B is L-valine, and R_1, A, R_3 and R_4 respectively are either
- benzyloxycarbonyl, L-valine, 4-methoxybenzyl and benzylamino, or
- 2-pyridylmethoxycarbonyl, L-valine, benzyl and benzylamino, or
- benzyloxycarbonyl, L-tert-leucine, benzyl and benzylamino, or
- D-phenyllactoyl, L-tert-leucine, benzyl, and benzylamino, or
- benzyloxycarbonyl, L-valine, benzyl and benzimidazol-2-ylmethylamino, or
- benzyloxycarbonyl, L-valine, 4-bromobenzyl and benzimidazol-2-ylmethylamino, or
- phenoxymethylcarbonyl, L-tert-leucine, benzyl and benzylamino,

in free form or, where such forms exist, in salt form.

8. A compound according to any one of claime 1 to 7 in free form or, where salt forms exist, in pharmaceutically acceptable salt form, for use as a pharmaceutical.

9. A process for the preparation of a compound according to claim 1 which comprises

a) submitting an epoxide of formula II



II

wherein the substituents are as defined in claim 1,

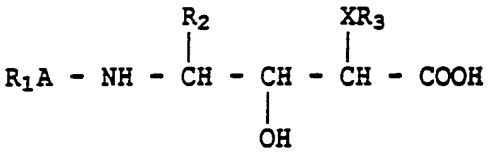
to ring opening in the presence of a compound of formula III

$$H - XR_3 \qquad III$$

wherein the substituents are as defined in claim 1, where indicated in a further reactive form; or

b) for the preparation of a compound of formula I wherein
$-BR_4$ is other than hydroxy [b_1], or
R_1 is other than hydrogen or HY- [b_2],
appropriately **substituting** a corresponding compound of formula I wherein $-CO-BR_4$ is carboxy or R_1 is hydrogen or HY-, e.g.

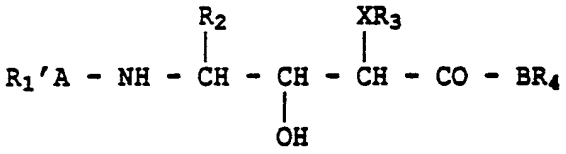
b_1) substituting a corresponding compound of formula Ia



Ia

wherein the substituents are as defined in claim 1, or

b_2) substituting a corresponding compound of formula Ib



Ib

wherein R_1' is hydrogen or HY- and
the other substituents are as defined in claim 1;
and where indicated **deprotecting or saponifying** a resultant compound of formula I in protected or esterified form,
and recovering the resultant compound of formula I in free form or, where such forms exist, in salt form.

10. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 in free form or, where salt forms exist, in pharmaceutically acceptable salt form, together with at least one pharmaceutically acceptable carrier or diluent.

INTERNATIONAL SEARCH REPORT

International Application N. PCT/EP 92/01471

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07C271/22; A61K31/325; C07K5/02; C07C237/22
A61K37/02

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07C ; C07K ; A61K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 412 350 (BAYER AG) 13 February 1991 see claims ---	1-10

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
11 SEPTEMBER 1992	25.09.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SANCHEZ GARCIA J.M.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9201471 SA 61130

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 11/09/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0412350	13-02-91	DE-A-	4004820	25-04-91
		AU-A-	6019390	07-02-91
		CA-A-	2022692	06-02-91
		JP-A-	3081256	05-04-91
		US-A-	5095006	10-03-92